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# Optimizing the Use of Injectable Therapies for Type 2 Diabetes



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## LEARNING OBJECTIVES

1. Provide a comparison of updated recommendations for type 2 diabetes mellitus
2. Describe the benefits and limitations of combination therapy with a glucagon-like peptide-1 receptor agonist and basal insulin
3. Identify strategies to optimize the use of a glucagon-like peptide-1 receptor agonist or basal insulin
4. Describe patient education strategies regarding the rationale and role of injectable therapy in type 2 diabetes mellitus
5. Describe the rationale and role of injectable therapies in the management of patients with type 2 diabetes mellitus
6. Describe strategies for redesigning the office visit with a patient with type 2 diabetes mellitus to support patient self-management with injectable therapy
7. Describe factors to consider and strategies to implement for redesigning the diabetes office practice to support patient self-management with injectable therapy

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# Introduction

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By at least 1 indicator, the diabetes fight is becoming worse. The percentage of people with diabetes who achieved a glycosylated hemoglobin ($HbA_{1c}$) level <7.0% actually declined from 2003-2006 to 2007-2010 (57.0% vs 52.5%, respectively).[1] Furthermore, fewer people aged 20 to 64 years (48.9%) achieved glycemic control than did people aged ≥75 years (63.3%) during the years 2007 through 2010.[1] These trends are particularly alarming when one considers the increasing number of treatment options for type 2 diabetes mellitus (T2DM) and the widespread efforts to raise awareness about obesity and other risk factors for T2DM.

There are many reasons why it will be difficult to reach the Healthy People 2020 goal of 58.9% of persons with diabetes achieving $HbA_{1c}$ <7.0%.[2] More than one-third of US adults (35.7%) and 17% of children and adolescents are obese.[3] Less than half of adults (48%) meet current recommendations for physical activity and fewer than 3 in 10 high school students exercise at least 1 hour a day.[4] In addition, adherence rates with glucose-lowering medications over 6 to 24 months of treatment range from 52% to 85%.[5-7] While metformin is the most frequently used glucose-lowering therapy (prescribed during 54% of treatment visits for diabetes in 2007),[1] surveys conducted by the Primary Care Education Consortium show some uncertainty among primary care physicians about how to intensify glucose-lowering therapy beyond metformin (unpublished results). In fact, only one-quarter of all patients with diabetes are treated with insulin.[8] Of these, only 30% achieve $HbA_{1c}$ <7.0%.[1] Possible reasons for the low rate of glycemic control are poor self-management skills and low adherence rates. In addition, people treated with insulin generally have more advanced disease, which may make attaining glycemic control biologically difficult.[1]

Within the past 2 years, the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists (AACE) have issued updated treatment guidelines for managing patients with T2DM.[9,10] Both of these guidelines are less prescriptive than previous versions and emphasize the importance of individualizing treatment. Also, the recommended roles for 2 injectable glucose-lowering agents, specifically insulin and the glucagon-like peptide-1 receptor (GLP-1R) agonists, have increased.[9,10] Insulin is preferred initially when $HbA_{1c}$ is >9.0% or when the patient experiences symptoms of hyperglycemia.[10] The GLP-1R agonists are preferred when avoidance of hypoglycemia or prevention of weight gain are treatment objectives.[9] Both insulin and GLP-1R agonists are recommended as components of dual and triple therapy as well.[9,10] A third injectable glucose-lowering agent available in the United States, pramlintide, is used in conjunction with prandial insulin. Pramlintide is not included in either the ADA/EASD or AACE treatment algorithms and is infrequently used in primary care because of its modest $HbA_{1c}$ reduction, gastrointestinal side effects, and injectable route of administration. Pramlintide will not be discussed in this supplement.

While the benefits of insulin and GLP-1R agonist therapy have led to a greater recommended role in the treatment of persons with T2DM, both have important barriers to their use. Among these are their subcutaneous route of administration, the need for patient education and ongoing support regarding self-injection, and costs to patients in comparison to generic oral medications. Other than vaccinations and some antibiotics, most primary care physicians are less familiar with injectable med-

ications. Additional barriers include the restrictive nature of intensive insulin treatment, which requires multiple injections at specific times of the day and in relation to meals, as well as the belief that insulin is the last resort if glucose levels cannot otherwise be managed.[11,12] Fear of hypoglycemia and feelings of failure remain concerns with insulin as well.

The growing importance of self-injectable medications for diabetes treatment parallels that for other diseases. This is an especially significant trend since patients are increasingly self-managing their diseases in the outpatient setting. This makes it necessary for primary care physicians to become more familiar with the role and use of injectable agents and to overcome the negative perceptions.

In diabetes, injectable medications and the devices now available for their administration are dramatically improved over previous products. The insulin analogs more closely mimic the actions of endogenous insulin and are associated with less hypoglycemia and weight gain than the human insulins.[13,14] The GLP-1R agonists mimic the actions of the incretin hormone GLP-1, which is estimated to account for approximately 70% of insulin secretion in response to oral glucose or a meal in healthy individuals.[15] Because of the glucose-dependent effects of GLP-1R agonists on insulin and glucagon secretion, the incidence and severity of hypoglycemia with these agents are low.[16-18] In addition, the GLP-1R agonists promote weight loss, primarily fat mass, in most patients.[16,17,19,20]

Major advances are also evident with the devices used to deliver injectable glucose-lowering agents. These advances include pens with shorter, smaller gauge, highly polished needles; pens that are easily portable and prefilled with medication; and 'dial-a-dose' gauges that are easy to read. These improved devices simplify administration, largely eliminate pain, and increase patient acceptance and adherence.[21-24]

The evolution in diabetes treatment makes it evident that injectable glucose-lowering medications are important treatment options across the spectrum of T2DM and provide a greater opportunity for treatment individualization. In the first article of this supplement, Helena Rodbard, MD, discusses the factors considered in the development of the 2012 ADA/EASD and 2013 AACE guidelines, as well as the combined use of basal insulin and a GLP-1R agonist. Next, Eden Miller, DO, provides strategies for initiating and individualizing insulin and GLP-1R agonist therapy, including recommendations for facilitating prior authorization. In the last 2 articles, real-world strategies are provided for redesigning care for patients with diabetes. In her article, Martha Funnell, MS, RN, CDE, provides insight into redesigning the physician-patient visit and discusses collaborative decision making and other approaches for engaging the patient in diabetes self-management with an injectable glucose-lowering agent. Edward Shahady, MD, takes a broader approach regarding the use of injectable glucose-lowering therapy, describing considerations in redesigning the office practice, including the participatory office practice, the Plan-Do-Study-Act model of quality improvement, accountable care organizations, and value-based care. Throughout the supplement, the authors provide links to resources they believe will be especially useful as you explore ways in which to use this important group of drugs in the management of patients with diabetes. ●

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# Increased Priority for Regimens Involving Incretin-Based and Insulin Therapy

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## INTRODUCTION

Practice guidelines and algorithms are important teaching tools and a means to help standardize approaches to clinical practice. For the management of glycemia in patients with type 2 diabetes mellitus (T2DM), several organizations, including the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the American Association of Clinical Endocrinologists (AACE), and the American College of Endocrinology (ACE) have developed guidelines and algorithms. The ADA and EASD jointly developed algorithms that were originally published in 2006,[1] updated in 2009,[2] and then presented as a position statement (not designated as either an algorithm or a guideline) in 2012.[3] The 2012 ADA/EASD position statement includes supplementary flowcharts that provide more focused recommendations when minimizing either the risk of hypoglycemia or weight gain or the cost of medications is of primary concern.

The AACE presented a guideline in 2002,[4] which was updated in 2007[5] and again in 2011.[6] The AACE and ACE developed an algorithm in 2009[7] in response to the ADA/EASD algorithms of 2006 and 2009. The 2009 AACE/ACE algorithm included a detailed explanation for its rationale, supporting evidence, references, a flowchart, and a table of the risks and benefits of various classes of therapies. In 2013, the AACE published a consensus statement that included a comprehensive diabetes management algorithm with diagrams for the management of glycemia, hypertension, dyslipidemia, obesity, and prediabetes (often with metabolic syndrome).[8]

A comparison of these guidelines, algorithms, and position/consensus statements is provided in **TABLE 1**.[2,3,7-9] This comparison shows that the 2009 AACE/ACE algorithm represented an advance relative to the 2009 ADA/EASD algorithm by virtue of being more inclusive. The 2009 AACE/ACE algorithm: (1) included more agents, especially the glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors; (2) recommended advancing therapy more rapidly (every 2 to 3 months); (3) selected a more aggressive goal for glycosylated hemoglobin ($HbA_{1c}$) when it was safe to do so, especially with respect to minimizing the risk of hypoglycemia; (4) emphasized the benefits of both rapid- and long-acting insulin analogs; and (5) downgraded the priorities for sulfonylureas, meglitinides, and thiazolidinediones. Bromocriptine was not included because of its limited efficacy, higher cost, and side effects.

The 2012 ADA/EASD position statement moved toward the recommendations and conclusions of the 2009 AACE/ACE algorithm and, in fact, endorsed many of them. The algorithm for glycemic management included in the 2013 AACE consensus statement, while displaying a rather dramatic graphic redesign of the 2009 AACE/ACE algorithm, remains essentially the same as the 2009 AACE/ACE algorithm. The main differences in the 2013 algorithm include the addition of bromocriptine, as well as the sodium glucose cotransporter-2 (SGLT-2) inhibitor group, the first of which was approved by the US Food and Drug Administration in March 2013.[10]

While control of weight, blood pressure, and blood lipids are vitally important management goals for patients with T2DM, the remainder of this review concerns the management of glycemia with the incretins—specifically, the GLP-1R agonists—and basal insulin, especially with respect to their combined use. Considerable clini-

**TABLE 1** **Comparison of the 2009 ADA/EASD algorithm, 2009 AACE/ACE algorithm, 2012 ADA/EASD position statement, and 2013 AACE consensus statement[9]**

| | 2009 ADA/EASD[2] | 2009 AACE/ACE[7] | 2012 ADA/EASD[3] | 2013 AACE[8] |
|---|---|---|---|---|
| **Nature of document** | **Algorithm** | **Algorithm** | **Position statement** | **Consensus statement** |
| **Target level for $HbA_{1c}$** | 7.0% (53 mmol/mol), or as low as possible without hypoglycemia | 6.5% (48 mmol/mol), with caveats | <7% (53 mmol/mol)[a] 6.0%–6.5%[b] 7.5%–8%[c] | ≤6.5% (48 mmol/mol) for healthy patients without concurrent illness and at low hypoglycemic risk |
| **Frequency of adjustment of regimen if not at goal** | 2–3 months | 2–3 months | 3–6 months | 3 months |
| **Lifestyle, diet, exercise, weight loss** | ✓ | ✓ | ✓ | ✓ |
| **Insulin therapy: basal, premixed, basal-bolus, with or without other agents** | ✓ | ✓ | ✓ | ✓ |
| **Metformin as preferred agent for monotherapy** | ✓ | ✓ | ✓ | ✓ |
| **Summary of risks and benefits for different classes of therapy** | ✓ | ✓ | ✓ | ✓ |
| **Specificity of advice for therapeutic agents** | High: algorithm with specified order for selection of agents and regimens | High: algorithm with specified order for selection of agents and regimens, with rationale | Low: Fig. 2 states "order not meant to specify any specific preference" | High: algorithm with specified order for selection of agents and regimens, with rationale |
| **Priority for sulfonylureas** | High (used in dual and triple therapy) | Low (because of hypoglycemia, weight gain, short duration of effectiveness); not recommended for monotherapy | No specific preferences (first option listed for dual and triple therapy in Fig. 2) | Low (because of hypoglycemia, weight gain, short duration of effectiveness); use with caution for monotherapy |
| **Priority for thiazolidinediones** | High (second of 5 options) | Low (because of weight gain, CHF, fractures) | No specific preferences (second option listed for dual and triple therapy in Fig. 2) | Low (because of weight gain, CHF, fractures) |
| **Priority for incretin-based therapies: DPP-4 inhibitors or GLP-1R agonists** | DPP-4 inhibitors: "insufficient experience" GLP-1R agonists: "Tier 2: less well-validated" | High (high efficacy and excellent safety, low risk of hypoglycemia) | No specific preferences | High (high efficacy and excellent safety, low risk of hypoglycemia) |
| **Priority for basal insulin** | "Tier 2: less well-validated" | High | High | High |
| **Preference for insulin analogs (rapid- and long-acting) relative to regular and NPH insulins** | None (no discussion of rapid- and long-acting insulin analogs) | High (regular and NPH insulins not recommended: Table A1) | Ambiguous, no preference stated | High (regular and NPH insulins not recommended: Table A1) |
| **Colesevelam** | Not considered | Included | Mentioned briefly (in Table 1, but not in Fig. 2) | Included |
| **Bromocriptine** | Not available | Not included | Included, low priority | Included |
| **Alpha-glucosidase inhibitors** | Not considered | Included | Mentioned briefly (in Table 1, but not in Fig. 2) | Included |
| **Sensitivity to cost of medication** | High | Low | High | Low |
| **Sensitivity to total cost of care** | Not discussed | High | Not discussed | High |

(continued)

**TABLE 1 CONTINUED**

**Comparison of the 2009 ADA/EASD algorithm, 2009 AACE/ACE algorithm, 2012 ADA/EASD position statement, and 2013 AACE consensus statement[9]**

| | 2009 ADA/EASD[2] | 2009 AACE/ACE[7] | 2012 ADA/EASD[3] | 2013 AACE[8] |
|---|---|---|---|---|
| **Nature of document** | **Algorithm** | **Algorithm** | **Position statement** | **Consensus statement** |
| **Number of therapeutic classes considered[d]** | 5 (Fig. 2) | 11 (Table 1) | 7 (Fig. 2) | 12 |
| **Number of regimens considered[d]** | 8 (Fig. 2) | 22 (Fig. 1) | 14 (Fig. 2) | 56+ |
| **Monotherapy regimens[d]** | 1 (metformin only) | 5 (metformin + 4 options) | 1 (metformin only) | 7 (metformin + 6 options) |
| **Dual-therapy regimens[d]** | 3 | 9<br>(14, if insulin is included) | 5 | 9, if metformin is obligatory[e,f]<br>35, if all possible combinations are permitted |
| **Triple-therapy regimens[d]** | 4 | 7<br>(16, if insulin is included) | 8 | 35, if metformin is obligatory[f,g]<br>84, if all possible combinations are permitted |
| **Initiation of therapy with dual therapy** | Not considered | If $HbA_{1c}$ 7.6%–9.0% (60–75 mmol/mol) | If $HbA_{1c}$ ≥9% (≥75 mmol/mol) | If $HbA_{1c}$ ≥7.5% (≥58 mmol/mol) |
| **Initiation of therapy with insulin or triple therapy** | Not considered | If $HbA_{1c}$ >9% (>75 mmol/mol) | If $HbA_{1c}$ ≥10% (≥86 mmol/mol) | If $HbA_{1c}$ >9% (>75 mmol/mol) |

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; EASD, European Association for the Study of Diabetes; GLP-1R, glucagon-like peptide-1 receptor; $HbA_{1c}$, glycosylated hemoglobin; NPH, neutral protamine Hagedorn.

[a] $HbA_{1c}$ target of 7.0% (53 mmol/mol), in general, to reduce incidence of microvascular disease.

[b] For selected patients (short disease duration, long life expectancy, no significant cardiovascular disease).

[c] For selected patients (if severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions or inability to achieve desired target).

[d] In main treatment flowchart.

[e] 35, if all possible combinations are considered.

[f] AACE/ACE 2013 algorithm[7] implicitly permits the combination of 7 agents used in monotherapy and any of 9 agents used for dual and triple therapy, giving rise to numerous possible regimens.

[g] 84, if all possible combinations are considered.



cal experience with this combination has emerged since the publication of the 2009 AACE/ACE algorithm and the 2012 ADA/EASD position statement.

## PATIENT SELECTION: ROLE OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

As reflected in both the 2012 ADA/EASD position statement and the 2013 AACE consensus statement, the unique pharmacologic profile of the GLP-1R agonists makes this class of glucose-lowering agents an excellent option for many patients who do not achieve adequate glycemic control with lifestyle modification and metformin, particularly when either hypoglycemia or weight gain is of special concern.

Furthermore, the nonglycemic effects of the GLP-1R agonists may provide important benefits because of the close association between T2DM and cardiovascular disease. In preclinical studies, GLP-1R agonists have demonstrated cardioprotective effects in animal models of coronary insufficiency and acute coronary experimental occlusion.[11,12] A small improvement in systolic and diastolic blood pressure has been observed with the GLP-1R agonists.[13,14] Small improvements in the lipid profile have also been observed, with the greatest reductions seen in the triglyceride level (range: 0 to 40 mg/dL).[15-25] Liraglutide has been shown to suppress the mean postprandial response for triglycerides from 0 to 8 hours following a fat-rich meal.[26] Long-term cardiovascular outcome studies with the GLP-1R agonists and DPP-4 inhibitors are currently in progress.[27-31]

The GLP-1R agonists are generally considered to address a key step in the pathogenesis of T2DM: pancreatic beta-cell dysfunction. Studies of rat and mouse models indicate that there is a slowing of beta-cell apoptosis.[32-35] However, in

human studies, there are conflicting data regarding a number of measures of pancreatic beta-cell function.[14,16,18,36-38]

## PATIENT SELECTION: ROLE OF INSULIN

Insulin is the most physiologic treatment option available and the form of therapy with which clinicians have the most experience. Since it has potentially unlimited glucose-lowering efficacy, insulin can be used for essentially all levels of hyperglycemia. Insulin (with or without other agents) is recommended as initial therapy by AACE for drug-naive patients with symptoms of hyperglycemia and $HbA_{1c}$ >9.0%[7,8] and by ADA/EASD for $HbA_{1c}$ >10.0%.[3] It is indicated if prior therapy with dual or triple therapy has failed to achieve the desired $HbA_{1c}$ target for a given patient.

In patients who do not achieve adequate glycemic control with lifestyle modification and metformin, basal insulin is 1 option recommended as a component of dual or triple therapy.[1-3,8] Basal insulin is especially useful for patients who have persistently elevated fasting plasma glucose (FPG) levels, whereas prandial insulin is used to target postprandial hyperglycemia. Insulin is important in patients with limited pancreatic beta-cell reserve (typically observed in longstanding T2DM). Intensive glycemic control with insulin was also shown to reduce the risk of microvascular complications in the United Kingdom Prospective Diabetes Study[39] and in the Kumamoto study.[40]

Insulin may be prescribed using 1 of 5 treatment options: (1) basal insulin only; (2) prandial insulin only; (3) a basal-bolus regimen (basal insulin combined with 3 injections per day of prandial insulin before meals); (4) a stepwise regimen involving basal insulin and 1, 2, or 3 injections per day of prandial insulin before the larger meals; or (5) a premixed insulin regimen, using a combination of a rapid-acting insulin analog and an intermediate-acting insulin analog (complexed with protamine).

Any of these 5 insulin regimens may be used alone or in combination with other agents. Combination therapy with insulin and an insulin sensitizer like metformin is often advantageous; however, insulin combined with a sulfonylurea or a meglitinide can result in a significant increase in the risk of hypoglycemia, weight gain, and fluid retention and, therefore, is not recommended. The use of insulin with a thiazolidinedione often leads to weight gain and fluid retention and may increase the risk for congestive heart failure. When combined with a GLP-1R agonist, the dose of insulin should be reduced to lower the risk of hypoglycemia.

## PATIENT SELECTION: ROLE OF A GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST PLUS BASAL INSULIN

When selecting combination glucose-lowering therapy, it is recommended that the agents chosen have complementary mechanisms of action.[3,8] The incretin system exerts unique actions to regulate glucose homeostasis, accounting for up to 70% of insulin secretion in response to oral glucose or a meal in healthy individuals.[41] Exenatide extended-release and liraglutide exert greater effects on FPG than exenatide BID, while the shorter-acting exenatide BID formulation exerts greater effects on postprandial glucose (PPG) than exenatide extended-release or liraglutide.[18,42-44] The combination of a GLP-1R agonist and basal insulin would be desirable when the goal is to avoid or minimize weight gain or to minimize the risk of hypoglycemia that can occur with basal insulin.[3,7,8]

The glycemic benefits resulting from the combination of a GLP-1R agonist and basal insulin have been demonstrated in 5 prospective clinical trials and several retrospective analyses.[45-57] The prospective trials show significantly greater reductions in $HbA_{1c}$ levels with the combination of a GLP-1R agonist and basal insulin than with either a GLP-1R agonist or basal insulin alone (**TABLE 2**).[45-49] In these studies, more patients who had not already achieved an $HbA_{1c}$<7% on 1 agent achieved this goal with the combination of a GLP-1R agonist and basal insulin.

The reduction in $HbA_{1c}$ with exenatide BID was associated with a significantly greater reduction in PPG than in FPG.[45,46] Major hypoglycemia, where the patient is unable to self-treat, was not observed in subjects receiving exenatide BID plus insulin glargine.[45,46] It was also not observed in patients receiving liraglutide plus insulin, in contrast to 2 episodes reported in those who did not receive liraglutide, but whose insulin doses were increased to improve glycemic control.[49] In 2 trials, minor hypoglycemia, where the patient is able to self-treat, occurred more frequently with the GLP-1R agonist plus basal insulin combination than with either a GLP-1R agonist or basal insulin alone.[45,47] However, in a third trial, minor hypoglycemia was significantly less frequent in those treated with liraglutide plus insulin than in those who did not receive liraglutide and whose dose of insulin was increased (11.9% vs 31%, respectively; $P = .033$).[49] In 3 trials, the combination of a GLP-1R agonist plus basal insulin resulted in a 0.16 to 1.78 kg weight *loss* compared with a 0.4 to 0.96 kg weight *gain* with basal insulin alone.[45-47] In a fourth trial, triple therapy, with basal insulin added to liraglutide plus metformin, led to significantly less weight loss over 52 weeks than did dual therapy with liraglutide plus metformin (–0.05 kg vs –1.02 kg, respectively; $P = .04$).

In a 12-week trial, adding liraglutide to an insulin regimen allowed a 66% reduction in the total daily insulin dose, from 41.2 to 14.0 U per day.[49] Other prospective trials have not confirmed this finding, possibly because of study designs that required upward titration of insulin to achieve glycemic goals.[45,46] In the 12-week trial, for subjects who did not receive liraglutide but for whom the dose of insulin was

**TABLE 2** **Glycemic outcomes for combined therapy with a long-acting basal insulin analog and a glucagon-like peptide-1 receptor agonist**

| Study description | Treatment | Change from baseline | | | | |
|---|---|---|---|---|---|---|
| | | $HbA_{1c}$ (%) | FPG (mg/dL) | PPG (mg/dL) | | |
| Arnolds 2010[45]<br>Length: 4 wks<br>N = 48<br>Baseline (mean): $HbA_{1c}$ 7.9%-8.4%; BMI 31.2-32.4 kg/m$^2$<br>Pre-study therapy: Basal insulin 32.3-40.3 U/d or metformin ± SU | After run-in: metformin + insulin glargine to achieve FPG <100 mg/dL in combination with:<br>Exenatide 5 mcg BID x 2 wks, then 10 mcg BID x 2 wks<br>or | -1.80[a] | -12 | 606[a,b] | | |
| | Sitagliptin 100 mg QD<br>or | -1.49 | -12 | 612[a,b] | | |
| | Placebo | -1.23 | -5 | 728[b] | | |
| Buse 2011[46]<br>Length: 30 wks<br>N = 261<br>Baseline (mean): $HbA_{1c}$ 8.3%-8.5%; BMI 33-34 kg/m$^2$<br>Pre-study therapy: Insulin glargine 47.4-49.5 U/d ± metformin ± pioglitazone | Insulin glargine to achieve FPG <100 mg/dL ± metformin ± pioglitazone in combination with:<br>Exenatide 5 mcg BID x 4 wks, then 10 mcg BID<br>or | -1.74[c] | -29 | Morning<br>-36[c] | Midday<br>-9 | Evening<br>-29[c] |
| | Placebo | -1.04 | -27 | -4 | -4 | 2 |
| DeVries 2012[47]<br>Rosenstock 2013[48]<br>Length: 26 wks (including 12-wk run-in), followed by 26-wk extension<br>N = 988<br>Baseline (mean): $HbA_{1c}$ 7.7%-8.3%; BMI 34-35 kg/m$^2$<br>Pre-study therapy: Metformin ± SU<br>12-wk run-in: SU discontinued; added liraglutide 0.6 mg QD x 1 wk, then 1.2 mg QD x 1 wk, then 1.8 mg QD x 10 wks | After run-in:<br>If $HbA_{1c}$ ≥7.0%, then: metformin + liraglutide 1.8 mg QD continued (RC group)<br>or | 0.02 | -14 | NR | | |
| | Metformin + liraglutide 1.8 mg QD + insulin detemir QHS to achieve FPG 74-108 mg/dL (RT group) | -0.51[d] | -38[d] | NR | | |
| | If $HbA_{1c}$ <7.0%, then: metformin + liraglutide 1.8 mg QD continued (OB group) | 0.2 | -7.2 | NR | | |
| | At 26 wks, patients (N = 723) continued above treatment; those not on insulin detemir (RC and OB groups) with $HbA_{1c}$ ≥8.0% could add insulin detemir | Week 0 to 52: | Week 0 to 52: | | | |
| | RC group | 0.01 | -3 | NR | | |
| | RT group | -0.50[d] | -34[d] | NR | | |
| | OB group | 0.30 | 4 | NR | | |

(continued)

increased in order to achieve improved glycemic control, the total daily insulin dose increased 28%, from 41.6 to 53.5 U per day. Changes in body weight generally paralleled changes in total daily insulin dose. Subjects treated with insulin plus liraglutide lost 5.6 kg compared to a 2.0 kg weight gain in those treated with progressively increasing doses of insulin ($P < .01$).

There appear to be significant advantages to initiating treatment with a GLP-1R agonist *before* initiating insulin therapy. First, a GLP-1R agonist may be sufficient to achieve the desired glycemic goals in some patients. For example, in the prospective study by DeVries et al (**TABLE 2**),[47] 61% of patients achieved $HbA_{1c}$ <7.0% during the 12-week run-in with the addition and titration of liraglutide to metformin. Second, use of a GLP-1R agonist may result in the need for a lower dosage of insulin. Third, treatment with a GLP-1R agonist mitigates and usually reverses the weight gain otherwise observed with insulin therapy.

Considering the results of these studies, it may be possible to identify a preferred subset of the multitude of combinations of therapies recommended in the ADA/EASD

**TABLE 2 CONTINUED**

**Glycemic outcomes for combined therapy with a long-acting basal insulin analog and a glucagon-like peptide-1 receptor agonist**

| Study description | Treatment | Change from baseline | | |
|---|---|---|---|---|
| | | $HbA_{1c}$ (%) | FPG (mg/dL) | PPG (mg/dL) |
| Li 2012[49]<br>Length: 12 wks<br>N = 84<br>Baseline (mean): $HbA_{1c}$ 8.7%-8.8%; BMI 30 kg/m$^2$<br>Pre-study therapy:<br>Insulin (basal or premixed) 41.2-41.6 U/d ± oral agents | Insulin to achieve FPG ≤110 mg/dL and 2-h PPG ≤144 mg/dL ± oral agents in combination with:<br>Liraglutide 0.6 mg QD x 1wk, then 1.2 mg QD; 0%-30% reduction of insulin dose<br>or | -1.9 | -28 | -97 |
| | Insulin (dose increased to achieve FPG, 2-h PPG targets) | -1.8 | -30 | -82 |

Abbreviations: BID, twice daily; BMI, body mass index; FPG, fasting plasma glucose; $HbA_{1c}$, glycosylated hemoglobin; NR, not reported; OB, observational; PPG, postprandial glucose; QD, once daily; QHS, once daily in the evening/bedtime; RC, randomized, controlled; RT, randomized treatment; SU, sulfonylurea.

[a]*P* < .05 vs placebo.

[b]Average postprandial blood glucose excursion from 0 to 6 hours (mg/dL-h) at end of treatment.

[c]*P* < .001 vs placebo.

[d]*P* < .0001 vs placebo.

2012 position statement[3] and the AACE/ACE algorithm.[5-8] A GLP-1R agonist is often effective as a second agent following treatment initiation with metformin, assuming there are no contraindications, no treatment-associated serious adverse events, and if treatment-related gastrointestinal side effects are tolerated or resolve spontaneously.[5-8] Basal insulin is an effective third agent.

## SUMMARY

The ADA/EASD[1-3] and AACE guidelines[4-8] emphasize the importance of individualizing treatment to best meet each patient's situation. Metformin remains the preferred choice as initial therapy for most patients.[1-8] The 2009 AACE algorithm[7] elevated the role of incretin-based therapies (GLP-1R agonists and DPP-4 inhibitors) relative to previous algorithms[1,2] and this has been endorsed by subsequent algorithms and guidelines.[3,6,8] The incretin-based therapies and insulin therapy should be considered with very high priority.[3,7,8] Either incretin-based therapy or insulin therapy can be used as monotherapy or in combination with other agents. The GLP-1R agonists are especially useful when attempting to reduce the risk of hypoglycemia and when assisting the patient to achieve weight loss. Insulin therapy is especially useful when the $HbA_{1c}$ level is >9.0% or when symptoms of glucotoxicity are present.[1-3,5,8] Insulin is the recommended treatment when other agents fail to achieve the desired target levels for $HbA_{1c}$, FPG, and PPG.[1-8] The combination of a GLP-1R agonist with basal insulin can provide better glycemic control than either agent alone, with less weight gain and a markedly lower incidence of hypoglycemia than with use of basal insulin alone. ●


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# Individualizing Care with Injectable Glucose-Lowering Agents

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DISCLOSURES
Dr. Miller discloses that she is on the advisory boards for Abbott Laboratories, Eli Lilly and Company, and Janssen Pharmaceuticals, Inc. She discloses she is on the speakers' bureaus for Amylin Pharmaceuticals, LLC, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceuticals, Inc., and Novo Nordisk, Inc.

The roles of injectable glucose-lowering agents (ie, insulin, pramlintide, or a glucagon-like peptide-1 receptor [GLP-1R] agonist) in the management of patients with type 2 diabetes mellitus (T2DM) continue to grow (see *Increased Priority for Regimens Involving Incretin-Based and Insulin Therapy* in this supplement). Nonetheless, their use presents challenges. An industry-funded survey of 505 primary care physicians (PCPs) revealed that injectable agents, specifically insulin, are seen as more complex and requiring more intensive patient education.[1] However, the same survey found that 69% of PCPs reported that most patients found the demands of insulin therapy to be less than expected and 76% observed that most patients felt much better physically once they became accustomed to using insulin therapy. Furthermore, 88% of PCPs believed the benefits of insulin therapy outweighed the risks of hypoglycemia and weight gain.[1] As reported by 93% of PCPs, key barriers to insulin are the injectable route of administration and the importance of, and time needed for, patient education. This article offers strategies for overcoming barriers to the use of injectable glucose-lowering agents, specifically insulin and GLP-1R agonists, by streamlining their initiation and by both reducing the risk of, and managing, common adverse events.

## WHERE CAN I FIND THE TIME TO INITIATE INJECTABLE GLUCOSE-LOWERING THERAPY?

Many reasons are given by PCPs for not initiating injectable glucose-lowering therapy, usually insulin, in patients with T2DM.[1] Among these, the multiple issues to be addressed during the short time of an office visit is one of the most commonly cited. While time constraints are real issues to address strategically, avoiding the use of injectable glucose-lowering therapy actually may prolong inadequate glycemic control and lead to more frequent and longer patient visits in an attempt to achieve that control with less effective agents. Acquiring the necessary knowledge and assembling the appropriate resources will enable the PCP to offer injectable glucose-lowering therapy as another of several treatment options for the management of patients with T2DM. These resources include other health care professionals as part of the patient's diabetes care team and related patient education materials.

Numerous resources are available to guide PCPs in the initiation and intensification of injectable glucose-lowering therapy with insulin or the GLP-1R agonists to achieve acceptable glucose control. Physicians and their diabetes care teams can use tools, patient education materials, and other resources developed by medical associations, medical organizations, government agencies, and manufacturers. Some of the tools and resources currently available can be used to quickly guide adjustments in therapy or provide education during a patient's office visit, while others can be used by the patient for learning at home. The following organizations offer sources of patient information.

- **American Association of Clinical Endocrinologists**
  http://outpatient.aace.com/
- **American Diabetes Association**
  http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/

- **American Association of Diabetes Educators** http://www.diabeteseducator.org/DiabetesEducation/Patient_Resources/
- **Academy of Nutrition and Dietetics** http://dbcms.s3.amazonaws.com/media/files/83de03de-c376-453d-aae0-bec014efc508/6403%20Advanced%20Insulin%20Management%20Final.pdf

The diabetes care team can be an important resource to both the physician and the patient. Whether organized formally or working informally with the physician, the team can minimize the amount of time a physician needs to spend providing patient education and follow up. At the same time, the patient can benefit from the special skills and knowledge that the nonphysician members of the team can provide. Team members may be staff within the physician's office or other health care providers located within the community. Team members may include a nurse, physician assistant/nurse practitioner, pharmacist, registered dietitian, and certified diabetes educator. It is important that team members work collaboratively and focus on the management goals established by the physician.

## HOW SHOULD THERAPY WITH INSULIN OR A GLP-1R AGONIST BE INITIATED AND TITRATED?

According to the 2013 comprehensive diabetes management algorithm developed by the American Association of Clinical Endocrinologists (AACE), a GLP-1R agonist is recommended as a second choice to metformin for monotherapy of a patient with a glycosylated hemoglobin ($HbA_{1c}$) level <7.5%, while basal insulin is recommended for a patient with symptoms of hyperglycemia and $HbA_{1c}$ >9.0% (**FIGURE**).[2] A GLP-1R agonist is not recommended as first-line therapy for patients inadequately controlled on diet and exercise.[3,4] Both a GLP-1R agonist and basal insulin are also options for dual or triple therapy for a patient with $HbA_{1c}$ ≥7.5%.[2] Therapy is generally initiated with basal insulin, preferably a long-acting analog, such as insulin detemir or insulin glargine, rather than neutral protamine Hagedorn (NPH) insulin. According to the AACE algorithm, the initial dose of basal insulin is dependent on the initial $HbA_{1c}$ level. Using a treat-to-target approach, therapy is adjusted every 2 to 3 days based on self-monitoring of blood glucose to achieve and maintain the individualized glycemic target. The AACE provides additional guidance for the management of patients with T2DM with insulin in their Diabetes Resource Center (http://outpatient.aace.com/type-2-diabetes/treatment). The Endocrine Society offers an interactive tutorial that guides adjustments of prandial or premixed insulin (http://www.accurateinsulin.org/). Other organizations have also developed algorithms for initiating or titrating insulin therapy.

- **American Diabetes Association** http://care.diabetesjournals.org/content/35/6/1364.full.pdf+html
- **California Diabetes Program** http://www.caldiabetes.org/content_display.cfm?contentID=1274&cameFromSearch=yes
- **Indian Health Service** http://www.ihs.gov/MedicalPrograms/Diabetes/index.cfm?module=toolsGCHowToInsulin
- **Texas Department of State Health Services** http://www.dshs.state.tx.us/diabetes/pdf/toolkit/appendix.pdf

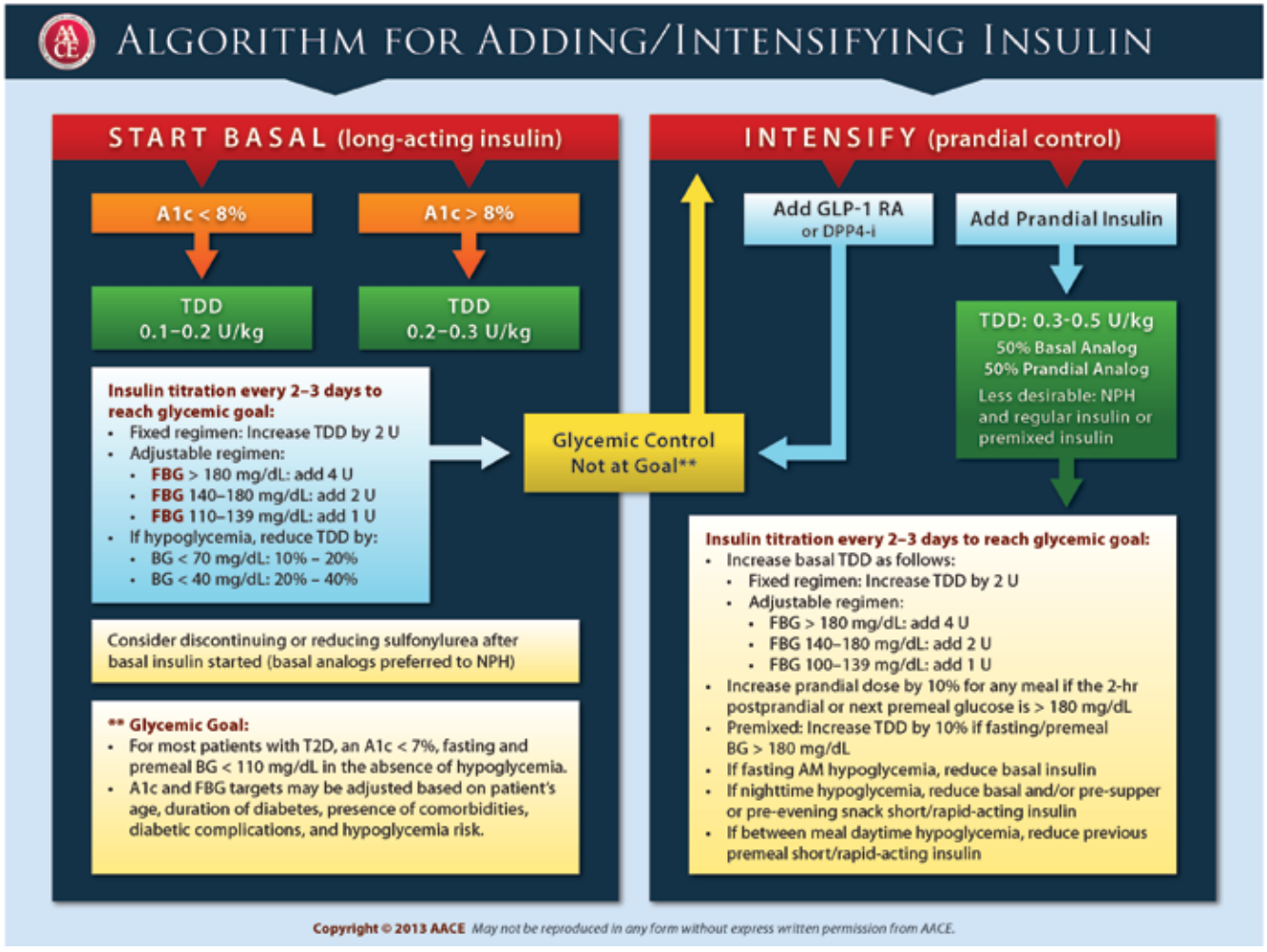
Individual clinicians have offered their own recommendations as well,[5,6] and smartphone applications, some of which calculate and track insulin doses, are also available.[7]

For patients who do not achieve their glycemic target with optimized basal insulin, the addition of prandial insulin, a GLP-1R agonist, or a dipeptidyl peptidase-4 (DPP-4) inhibitor to intensify therapy is recommended (see *Increased Priority for Regimens Involving Incretin-Based and Insulin Therapy* in this supplement).[2]

At present, practice guidelines do not provide recommendations for the initiation and intensification of therapy with a GLP-1R agonist. Therefore, recommendations found in the medications' prescribing information should be followed. Liraglutide (taken once daily) and exenatide once weekly (QW) should be administered at the same time of the day irrespective of meals, while exenatide twice daily (BID) is to be administered within 60 minutes prior to the 2 main meals of the day, approximately 6 hours or more apart. The GLP-1R agonists are administered subcutaneously in the abdomen, thigh, or upper arm. Exenatide BID is initiated at a dose of 5 mcg twice daily and increased to 10 mcg twice daily after 1 month, based on clinical response.[8] Exenatide QW is administered immediately after the powder is reconstituted at a dose of 2 mg once every 7 days.[3] Liraglutide is initiated at a dose of 0.6 mg once daily for 1 week and then increased to 1.2 mg once daily. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg once daily.[4]

The onset of glucose lowering occurs within a few days with exenatide BID and liraglutide[9-11]; with exenatide QW, however, it may take up to 2 weeks for the onset of glucose lowering because of a delay in achieving a therapeutic blood concentration until 2 to 5 weeks after initiation of therapy.[12,13] It is important to inform patients about the onset of glycemic lowering with these agents in order to manage their expectations. Resources regarding the use of the GLP-1R agonists have been developed by their manufacturers (exenatide BID: http://www.byettahcp.com/; exenatide extended-release: http://www.bydureonhcp.com/; liraglutide: http://www.victozapro.com).

**FIGURE** **American Association of Clinical Endocrinologists algorithm for adding and intensifying insulin therapy[2]**




Abbreviations: A1c, glycated hemoglobin; BG, blood glucose; DPP4-i, dipeptidyl peptidase-4 inhibitor; FBG, fasting blood glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; T2D, type 2 diabetes mellitus; TDD, total daily dose.

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## WHAT CAN BE DONE TO STREAMLINE THE PROCESS FOR PRIOR AUTHORIZATION?

There is no doubt that prior authorization (PA) for drugs and tests is viewed negatively by physicians. A 2010 survey by the American Medical Association (AMA) found that 95% of physicians surveyed (N = 2400) felt that eliminating hassles caused by insurer PA requirements is important.[14] This finding is not surprising given that more than half of physicians (57%) reported experiencing a 20% rejection rate from insurers on first-time PA requests for drugs and 69% typically waited several days to receive approval. A recent prospective study estimated that the annual cost for staff time spent on PA activities ranged from $2161 to $3430 per full-time physician; previous estimates exceeded $80,000.[15] While the true cost likely lies between these estimates, addressing the issue is a physician priority. The AMA survey also found that 75% of physicians felt that automating the PA process would help them manage their patients' care more efficiently. To address this issue, the AMA has developed a PA toolkit that may be helpful in assessing the impact of health information technology solutions on a physician's practice (http://www.ama-assn.org/ama/pub/physician-resources/practice-management-center/claims-revenue-cycle/prior-authorization.page). Automating the PA process is a goal of the AMA as part of its "Heal the Claims Process" campaign.[16]

While the forms and documentation required by insurers for PA varies, the importance of providing complete and accurate information cannot be overemphasized. Relevant

laboratory reports and documentation of the patient's clinical course, including prior treatments and reasons for their failure, must be included. To simplify the PA process, it may be helpful to embed the PA in the patient's electronic health record, either as a dictated note or in the patient's progress note. In the plan section of the progress note, it can be stated "Let this note serve as a PA for ABC Rx because…." This note and supporting documentation can be included with the information sent to the insurance company.

## WHAT TIPS CAN BE EMPLOYED TO ADDRESS OTHER ISSUES WITH THE USE OF INJECTABLE GLUCOSE-LOWERING THERAPIES?

Questions related to the administration and storage of injectable glucose-lowering therapies are common. While following manufacturers' recommendations is important, answers to some questions have been learned from first-hand experience. An important point to keep in mind is that if the patient is having any difficulty with self-administration, they should be asked to demonstrate their technique in the physician's office. In fact, it is suggested that the patient administer the first dose of the GLP-1R agonist in the office so that initial difficulties can be identified and resolved. The importance of having the patient periodically demonstrate his or her technique *without prompting* is evident in the following example: a patient, who reported having difficulty penetrating the skin, was found to have failed to remove the needle cap prior to attempting to administer the dose.

### Mixing insulins

The availability of a wide variety of premixed insulin formulations has limited, but not eliminated, the practice of mixing different insulins. It should be remembered that the basal insulin analogs detemir and glargine *cannot be mixed* with any other insulin, while NPH insulin can be mixed with a prandial insulin (eg, aspart, glulisine, lispro, regular human) in the same syringe. The prandial insulin should be drawn into the syringe first, followed by the NPH insulin. The syringe should then be gently inverted prior to injection.

### Leakage and bleeding at injection site

While needles for subcutaneous injection are available in different lengths, the use of needles shorter than 8 mm is generally appropriate.[17,18] Should backflow or leakage of more than a drop or 2 occur at the injection site, use of the 8 mm needle is advised. An occasional drop or two of blood at the injection site is common, but if bleeding occurs consistently, it is likely that the injection is penetrating into capillaries. In this case, use of a shorter or longer needle is advised.

### Storage

Insulin and the GLP-1R agonists should be stored at a controlled temperature according to manufacturers' recommendations, avoiding both freezing temperatures and heat above normal room temperature (**TABLE 1**).[3,4,8,19-27] This is particularly important if the patient is traveling for an extended time period (ie, more than 30 days). Once the medication package has been removed from the refrigerator, the insulin or GLP-1R agonist can be stored at room temperature for up to 28 days (longer for a few products), but it must be kept out of direct sunlight and in a cool, dry location.

Patients should be educated about the importance of visually inspecting their medication and devices prior to each use. It is possible for the medication to become tinged with blood. If there is a slight tinge, experience suggests that the medication can still be used. If the patient is in doubt, if the medication is more than slightly tinged, or if it contains debris or a precipitate, the patient should be told not to use the medication and to consult a physician, pharmacist, or nurse.

## WHAT STRATEGIES CAN BE USED TO MINIMIZE THE OCCURRENCE OF HYPOGLYCEMIA WITH INJECTABLE GLUCOSE-LOWERING AGENTS?

When considering the addition of injectable glucose-lowering therapy, it is important to consider the risk of treatment-related hypoglycemia (high risk with insulin, low risk with GLP-1R agonists),[2] determine a patient's risk for hypoglycemia, and assess his or her motivation for and likelihood of adherence. Prior to therapy, patients also should be evaluated for the presence of liver or kidney disease. Liver disease can contribute to decreased glucose production, while renal dysfunction prolongs the duration of action and slows the clearance of insulin and exenatide, but not liraglutide. One of the risk factors to consider when selecting or adjusting injectable glucose-lowering therapy is the glycemic target, since more intensive glucose lowering can result in more frequent hypoglycemia with insulin and pramlintide.[28,29]

Strategies to prevent or minimize the occurrence of hypoglycemia should be discussed with every patient at the time that glucose-lowering therapy is initiated or adjusted. Patients should be educated about conditions that place them at risk of hypoglycemia, such as decreased glucose intake or absorption (eg, a missed or delayed meal, vomiting, gastroenteritis) or increased glucose utilization (eg, physical exercise). They should also be educated about the signs and symptoms of hypoglycemia and actions to take should it occur. Periodically reminding them about this information is important and including it in a written action plan can be helpful (http://www.diabetes.org/

**TABLE 1** **Storage of glucagon-like peptide-1 receptor agonists and insulins**[3,4,8,19-27]

| | Trade name | Prior to first use | | After first use | | Sunlight | Other |
|---|---|---|---|---|---|---|---|
| | | Temperature (°F) | Expiration | Temperature (°F) | Expiration | | |
| **Glucagon-like peptide-1 receptor agonists** | | | | | | | |
| **Exenatide BID** | Byetta | 36-46 | As marked on unit | 36-77 | 30 days | Avoid | Do not freeze; store without needle attached |
| **Exenatide QW** | Bydureon | 36-46 | As marked on unit | Use immediately after preparation of suspension | | | Do not freeze |
| | | RT 68-77 | Up to 4 weeks | | | | |
| **Liraglutide** | Victoza | 36-46 | As marked on unit | Refrigerated (36-46) or controlled RT (59-86) | 30 days | | Do not freeze; store without needle attached |
| **Prandial insulins** | | | | | | | |
| **Aspart** | NovoLog | 36-46 | As marked on unit | RT <86 (vial, cartridge, FlexPen, KwikPen) | 28 days | Avoid | Do not freeze; store without needle attached |
| | | RT <86 | 28 days | | | | |
| **Glulisine** | Apidra | 36-46 | As marked on unit | RT or refrigerated (36-77) (vial); RT <77 (cartridge in OptiClik, SoloStar) | 28 days | | Do not freeze |
| | | RT≤77 | 28 days | | | | |
| **Lispro** | Humalog | 36-46 | As marked on unit | RT or refrigerated <86 (vial); RT <86 (cartridge, pen, KwikPen) | 28 days | | Do not freeze |
| | | RT <86 | 28 days | | | | |
| **Regular human** | Humulin R | 36-46 | As marked on unit | RT <86 (vial) | 31 days | | Do not freeze |
| | Novolin R | 36-46 | As marked on unit | RT ≤77 | 42 days | | Do not freeze |
| | | RT ≤77 | 42 days | | | | |
| **Basal insulins** | | | | | | | |
| **Neutral protamine Hagedorn** | Humulin N | 36-46 (vial, pen) | As marked on unit | RT or refrigerated, 36-86 (vial); RT <86 (pen) | Expiration date (vial); 14 days (pen) | Avoid | Do not freeze; store pen without needle attached |
| | Novolin N | 36-46 | As marked on unit | RT <77 | 42 days | | Do not freeze |
| | | RT ≤77 | 42 days | | | | |
| **Detemir** | Levemir | 36-46 | As marked on unit | RT or refrigeration, 36-86 (vial); RT <86 (FlexPen) | 42 days | | Do not freeze; store pen without needle attached |
| | | RT <86 | 42 days | | | | |
| **Glargine** | Lantus | 36-46 | As marked on unit | RT or refrigeration, 36-86 (vial, cartridge); RT <86 (SoloStar, cartridge in OptiClik) | 28 days | | Do not freeze |

Abbreviations: BID, twice daily; RT, room temperature; QW, once weekly.

**TABLE 2** Relative risk of hypoglycemia among available glucose-lowering agents[2,30,31]

| AGI | Bromocriptine | Colesevelam | DPP-4 inhibitor | GLP-1R agonist | Insulin | Meglitinide | MET | Pramlintide | SGLT-2 inhibitor | SU | TZD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| + | + | + | + | + | ++++ | ++ | + | + | + | +++ | + |

Abbreviations: AGI, alpha-glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; MET, metformin; SGLT-2, sodium glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

+, no hypoglycemia; ++ infrequent hypoglycemia; +++ occasional hypoglycemia; ++++, frequent hypoglycemia.

assets/pdfs/schools/dmmp-form.pdf). The action plan should also contain a dosing algorithm and recommendations for self-monitoring of blood glucose. Patients should also be asked on a regular basis about habits that they have adopted to avoid hypoglycemia, such as eating a snack in the afternoon, at bedtime, or prior to driving a car. Family members and caregivers should be educated as well, as they may be the ones to recognize and initially manage a hypoglycemic episode (see Tenzer-Iglesias P, Shannon MH. *J Fam Pract*. 2012;61[10 suppl]: S1-S8, for additional information regarding educating patients about hypoglycemia).

Hypoglycemia is possible with each of the classes of glucose-lowering agents, especially when they are used in combination (**TABLE 2**).[2,30,31] For example, while the incidence of hypoglycemia is low with GLP-1R agonist monotherapy, the use of a GLP-1R agonist with a secretagogue increases the risk several-fold.[12,32-34] For this reason, the dose of the secretagogue should be reduced when used in combination with a GLP-1R agonist.

The choice of insulin type and formulation will also determine the risk of hypoglycemia. For example, rates of symptomatic, overall, and nocturnal hypoglycemia are lower with the basal insulin analogs (insulin detemir, insulin glargine) than with NPH insulin.[35] Consequently, the basal insulin analogs are recommended over NPH insulin.[2,31] Similarly, overall and severe hypoglycemia are less frequent with the prandial insulin analogs (insulin aspart, insulin glulisine, insulin lispro) than with regular human insulin.[36]

Finally, hypoglycemia unawareness should be considered in persons with frequent mild hypoglycemia or in those who have experienced an episode of severe hypoglycemia, since persons with hypoglycemia unawareness have a 6- to 17-fold increased risk of experiencing a severe hypoglycemic episode compared with those with normal hypoglycemia awareness.[37-39] For patients with hypoglycemia unawareness, completely avoiding a hypoglycemic episode for 2 to 3 weeks may be effective in reestablishing the altered biologic response to abnormal glucose counter-regulation.[40] Patient education intended to improve hypoglycemia awareness is also suggested.

## OTHER THAN INITIATING GLP-1R AGONIST THERAPY WITH A LOW DOSE FOLLOWED BY DOSE ESCALATION, WHAT CAN BE DONE TO REDUCE THE INCIDENCE AND SEVERITY OF GASTROINTESTINAL ADVERSE EVENTS?

Transient gastrointestinal adverse events observed with the initiation of GLP-1R agonists include constipation, diarrhea, dyspepsia, nausea, and vomiting.[3,4,8] Among these, nausea is the most frequent and troubling to patients, occurring in approximately one-quarter of patients; therefore, alerting patients to the possibility of experiencing nausea and assuring them that it is generally short-lived is important.[41] Nausea is usually mild and it generally peaks within 8 weeks of starting exenatide BID and within 2 to 8 weeks of starting liraglutide. Nausea resolves in all but about 10% of patients within 28 weeks with exenatide BID and within 4 to 8 weeks with liraglutide.[10,41-44] With exenatide QW, nausea also peaks early following initiation of treatment and resolves within 10 weeks in nearly all patients.[44,45] If nausea or vomiting occurs during dose escalation, the length of time over which the dose of exenatide BID or liraglutide is increased can be prolonged. Since there is no dose escalation with exenatide QW, this strategy does not apply; however, of the 3 GLP-1R agonists currently available, exenatide QW is the least likely to cause nausea.[12,44] Alternatively, the dose of exenatide BID or liraglutide can be temporarily reduced until the nausea and vomiting have resolved, at which time the dose can again be increased.

There are additional strategies that can be employed if nausea with GLP-1R agonist therapy becomes intolerable.[46-48] First, all patients treated with a GLP-1R agonist should be advised to stop eating when they feel full. It is worth noting that some patients with T2DM confuse a feeling of fullness with nausea. Patients also should be encouraged to eat smaller meals and to avoid high-fat meals. Second, the dose of exenatide BID can be taken closer to mealtime than the recommended 60 minutes. Third, for patients taking a GLP-1R agonist in combination with metformin, lowering the dose of metformin is often effective in reducing nausea. A fourth option is to consider switching from 1 GLP-1R agonist to another: experience from clinical trials shows that some patients who experienced persistent nausea with exenatide BID were able to tolerate exenatide QW or liraglu-

tide.[33,49] A final option is for patients to premedicate with an oral antiemetic before administering their GLP-1R agonist agent for up to a week or 2. Limited experience in healthy subjects (N = 120) showed that oral metoclopramide 10 mg with ondansetron 8 mg taken 30 minutes before administration of a single 10 mcg dose of exenatide BID resulted in a significant reduction in the incidence of nausea (16.7% vs 61.7%) and vomiting (6.7% vs 38.3%) over 24 hours compared with those who received no antiemetic therapy.[50]

## WHAT CAN BE DONE TO MINIMIZE WEIGHT GAIN ASSOCIATED WITH INSULIN THERAPY?

While the reasons for the weight gain observed with insulin therapy remain obscure, it may reflect a complex interaction of factors, such as food intake, exercise, stress, insulin resistance, the type of insulin being used, and the brain's perception of hunger and satiety. However, from a pragmatic point of view, the challenge is to match the dose(s) of insulin as closely as possible to the body's insulin needs throughout the course of the day. If too little insulin is administered, hyperglycemia persists. If too much insulin is administered, hypoglycemia occurs and a greater number of calories must be consumed to forestall a hypoglycemic episode. If a hypoglycemic episode, followed by food consumption, occurs frequently, weight gain is likely. It therefore becomes important to maintain, to the extent possible, a regular schedule of the factors that affect insulin requirements and blood glucose levels.

Among these factors, physical activity and dietary habits are 2 of the most important and serve as the cornerstones of overall diabetes management. In fact, 1 study found that the primary reason patients treated with insulin gained weight was physical inactivity.[51] Overall, those who gained weight had a poorer cardiometabolic profile than those who did not gain weight. Conversely, increased physical activity must be accompanied by an appropriate downward adjustment of the insulin dose. This adjustment must be guided by patient self-monitoring of blood glucose levels to avoid hypoglycemia. Since physical activity can affect glucose disposal and a patient's insulin requirement for several hours or longer after completion of the activity, infrequent episodes of physical activity can make control of blood glucose challenging.[52,53] Therefore, a regular schedule of physical activity is strongly advised for both weight and glycemic control. Similarly, good dietary habits, including not skipping meals, are important in maintaining effective glucose disposal and insulin requirements and in helping to avoid hypoglycemia, ingestion of excess calories, and subsequent weight gain. It may be helpful to recommend calorie counting to assist patients in fostering good dietary habits.

The choice of basal insulin also can affect weight gain. A meta-analysis of 46 randomized trials showed that body weight increased to a lesser degree with insulin detemir than with NPH insulin; there was no difference in weight gain between insulin glargine and NPH insulin.[54] Two studies included in the meta-analysis that directly compared insulin detemir and insulin glargine showed less weight gain with insulin detemir. In contrast, a separate pooled analysis of 22 trials in patients with T2DM treated with insulin detemir or insulin glargine over at least 20 weeks showed similar weight gain with insulin detemir and insulin glargine (1.7 vs 2.5 kg, respectively).[55] In another study, when weight gain was analyzed based on glycemic control, weight gain per 1.0% change in $HbA_{1c}$ was similar with insulin detemir and insulin glargine (1.2 vs 1.8 kg, respectively). A recent real-world retrospective analysis of US General Electric Centricity electronic medical records showed similar percent weight loss over 12 months or more with insulin detemir and insulin glargine in insulin-naive adults with T2DM (0.91% vs 0.65%, respectively).[56]

Other medications that are associated with weight gain should be avoided, if possible, in patients taking insulin. Other glucose-lowering agents associated with weight gain include the meglitinides, sulfonylureas, and thiazolidinediones.[2,31] Examples of nonglucose-lowering agents associated with weight gain include atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine); antidepressants (amitriptyline, mirtazapine, some serotonin selective reuptake inhibitors); mood stabilizer (lithium); and antiepileptics (carbamazepine, gabapentin, valproic acid).[57]

By comparison, the use of insulin in combination with metformin has been shown to result in weight loss or minimal weight gain.[58] Similarly, in 3 trials involving the combination of a basal insulin with a GLP-1R agonist, a weight loss of 0.16 to 1.78 kg was observed compared with a weight gain of 0.4 to 0.96 kg with basal insulin alone[59-61] (see *Increased Priority for Regimens Involving Incretin-Based and Insulin Therapy* in this supplement).

## CONCLUSION

Insulin and GLP-1R agonists are important treatment options for the management of patients with T2DM, yet provider and patient concerns limit their use. Effective strategies, including ongoing patient education, can be easily implemented to overcome concerns and streamline initiation and ongoing use of injectables. The use of a GLP-1R agonist, for example, is 1 strategy recommended when avoidance of hypoglycemia or weight gain is a specific treatment goal. ●


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# Engaging the Patient in Diabetes Self-Management

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DISCLOSURES
Ms. Funnell discloses that she is on the advisory boards for Animas Corporation/Lifescan, Inc., Bayer Diagnostics, Boehringer-Ingelheim GmbH, Bristol-Myers Squibb Company/AstraZeneca Diabetes, Eli Lilly and Company, GlaxoSmithKline, Halozyme Therapeutics, Inc., Hygeia, Inc., Intuity Medical, Inc., Johnson & Johnson Services, Inc., and Omada Health.

## CASE STUDY

Jenny S is a 48-year-old Caucasian female who only visits her primary care physician (PCP) when she has a major health concern or acute illness. Jenny presents with a complaint of increasing fatigue over the past few months, which has made it difficult to care for her family. She reports urinating 7 to 8 times/day and 2 to 3 episodes of blurred vision after eating large meals during the recent holidays. Physical examination shows that Jenny is obese (weight 85 kg, body mass index 32.2 kg/m$^2$) and has acanthosis nigricans on her neck and flexor surfaces. The remainder of her physical examination is normal. In-office glycosylated hemoglobin ($HbA_{1c}$) is 10.7% and a random glucose level is 264 mg/dL. A recent eye examination by her ophthalmologist revealed she has pre-proliferative retinopathy.

The PCP makes a diagnosis of type 2 diabetes mellitus (T2DM). Jenny is very tearful upon hearing the news because she has seen the effects of diabetes on several family members. The PCP asks Jenny about her fears, reassures her about improvements in therapies, and explains that he and others will work closely with her so she has the help she needs. He recommends initiating metformin and basal insulin. Jenny agrees to start metformin, but is hesitant about starting basal insulin, saying she is too upset and wants to think about it for a week or 2. The PCP asks Jenny if she would be willing to meet with the local diabetes educator to address her concerns and learn more about T2DM. Jenny agrees.

### *Follow-up visit*

At the follow-up visit 10 days later, Jenny's $HbA_{1c}$ is 10.7% and fasting blood glucose (FBG) is 152 mg/dL. Jenny indicates that the diabetes educator helped her understand more about diabetes and what she can do to prevent the complications. She also helped Jenny with her worries about weight gain and hypoglycemia and made her feel more confident about self-administering insulin. Jenny understands that keeping her blood glucose closer to normal will help her feel better and have more energy and will reduce the risk of complications. While Jenny expresses a willingness to start treatment with insulin and metformin and to begin to make some changes in her lifestyle, she indicates that she is feeling overwhelmed and fearful with all there is to do.

When developing a treatment plan, the American Association of Clinical Endocrinologists (AACE) recommends that the patient's $HbA_{1c}$ be a key consideration.[1] For $HbA_{1c}$ <7.5%, monotherapy, generally with metformin, is recommended. For $HbA_{1c}$ ≥7.5% but <9.0%, metformin in combination with another glucose-lowering agent is recommended.[1] While this approach should provide for more rapid glycemic control than monotherapy, the greater risk of drug-related adverse events dictates that therapy be individualized.

The hierarchy of usage recommended by the AACE is a glucagon-like peptide-1 receptor (GLP-1R) agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor, thiazolidinedione, or other glucose-lowering agent. Because Jenny's $HbA_{1c}$ is above 9.0% and she is experiencing symptoms of glucotoxicity, initial therapy with basal insulin with or without another glucose-lowering agent is recommended by the AACE (see *Increased Priority*

*for Regimens Involving Incretin-Based and Insulin Therapy* in this supplement).[1]

***Treatment plan:***

- Begin metformin 500 mg twice daily for 2 weeks, then increase to 850 mg twice daily
- Begin insulin detemir 17 U at dinner (0.2 U/kg x 85 kg); increase by 2 U every 3 days (maximum 25 U) to achieve FBG of 90 to 130 mg/dL
- Continue to work with the diabetes educator to address Jenny's fears, review insulin administration and blood glucose monitoring, and provide additional resources and support for Jenny's efforts
- Check blood glucose levels daily before breakfast
- Call office to report blood glucose readings in 2 weeks
- Follow-up visit in 1 month

## INTRODUCTION

As with many chronic diseases, the treatment of T2DM can be challenging for both the patient and the clinician. While knowledge of the pathophysiology and the multimodal treatment of T2DM form the basis of medical care, it is largely a self-managed disease.[2,3] As a consequence, the success or failure of patients to achieve recommended outcomes is greatly determined by their own knowledge as well as by their willingness and ability to engage in self-management. The clinician's primary role, therefore, is to provide support, information, and advice rather than to make decisions for the patient.

To effectively implement this role, it is essential for the clinician to establish a collaborative relationship with the patient and to engage the patient so that she can make informed decisions. In this case study, rather than taking the "do as I say" approach, the PCP senses Jenny's distress and asks Jenny to meet with the diabetes educator, who can help address Jenny's concerns. This approach is reasonable, given the limited time allotted for an office visit and the importance of initiating treatment considering Jenny's signs and symptoms. In addition, addressing Jenny's concerns helps develop a collaborative relationship between the PCP and the patient. It also makes it clear to Jenny that the PCP views her as an individual and that her care is focused on her abilities, values, and preferences so that she can effectively self-manage her T2DM.

Patient-centered medical care is a core principle of the chronic care model. The goal of this model is to enable patients to self-manage their disease by providing the necessary system and medical care framework to support both the patient and the health care team.[4] For many clinicians, fully implementing the chronic care model or the patient-centered medical home may require a redesign of their clinical practices, including the patient visit. Considerations regarding a redesign of the clinical practice are discussed in *Preparing for Success: Redesigning the Diabetes Office Practice* in this supplement. The remainder of this article focuses on redesigning the patient visit to support self-management. Emphasis is placed on injectable glucose-lowering therapy, specifically insulin or GLP-1R agonists.

## REDESIGNING THE PATIENT VISIT

The traditional office visit is primarily structured to provide care for an acute problem rather than ongoing care for a chronic disease. Because self-management plays a limited role in many acute problems, the traditional office visit does little to foster effective chronic disease care. Yet making the change from the acute care to the chronic care model and from clinician management to collaborative care and self-management is critical in T2DM. [5]

### Shared decision making

Shared decision making is a critical component of patient-centered care. Shared decision making is a collaborative process that allows patients and their providers to make health care decisions together, taking into account the best scientific evidence available as well as the patient's abilities, values, and preferences. It is a cost-effective approach that seeks both to fully inform patients about the risks and benefits of available treatments and to ensure their participation in management decisions. This is particularly relevant for the injectable glucose-lowering agents, since patients must be capable of giving themselves injections and willing to do so. In addition, patients taking insulin may need to calculate an appropriate dose and/or carbohydrate intake.[6]

Fundamental to this process is recognition of the patient as a person with a disease rather than simply as a disease with treatment targets. This concept is at the core of the 2012 American Diabetes Association/European Association for the Study of Diabetes and the 2013 American Association of Clinical Endocrinologists guidelines, both of which emphasize the importance of individualizing care.[1,7] The PCP in the case study has demonstrated the central role Jenny plays in her care by not immediately advancing his plan because of Jenny's reluctance to begin treatment; instead, he supports her with the involvement of other health care professionals. However, while many patients may want to be actively involved in their care, not all patients have the information or confidence needed to collaborate in the decision-making process. Therefore, determining the extent to which the patient may wish to or be able to participate in decision making is an important first step.

Similarly, the patient's willingness and ability to self-manage should also be assessed. It should be noted that

patients often wish to become more involved in their own care as they gain experience and feel more comfortable with self-management. A survey of 505 PCPs found that 69% reported that most patients found the demands of insulin therapy to be less than expected.[8] Sharing these types of experiences enables clinicians to help patients overcome their concerns and more confidently initiate injectable glucose-lowering therapy. It is also a reminder to avoid verbal and nonverbal cues that treatment with injectable glucose-lowering therapy is especially difficult or complex. Instead, patients should be assured that, as with any glucose-lowering agent, they will receive the support needed to be successful.

Beginning at the time of diagnosis, the roles for the PCP and the patient need to be discussed in order to set the stage for ongoing care. The discussion can start with the importance of the patient's role in the management of a demanding chronic disease, a description of the PCP's role as coach and advisor, and roles of other team members (eg, care manager, diabetes educator).[9] Education should be provided to help the patient understand that chronic disease care needs to be a true partnership that combines the clinician's medical knowledge with the patient's self-knowledge to create the most feasible and effective treatment plan possible. Conversations should be ongoing, particularly as the patient's treatment needs change, if there are changes in the patient's situation or priorities, or when a plan simply is not working from the perspective of either the patient or the clinician. Assuring the patient that he or she will be supported and provided with the resources needed is crucial for success of the plan.

Collaborative decision making draws upon the best available scientific evidence and the patient's abilities, preferences, goals, and values to develop a management plan. The best available evidence for any particular patient comes first and foremost from the patient as well as from other sources, ranging from clinical trials to the personal experiences of the clinician. To be effective, this discussion necessitates acknowledging uncertainty about the risks and benefits of each treatment option, conflicts among the scientific evidence, and how a particular treatment will affect an individual patient. A clinician's acknowledgment of both the uncertainty and the conflicts that exist may be helpful as the patient works to resolve the uncertainty and difficulties she may be experiencing in participating in the decision-making process about her care.[5]

To successfully engage in shared decision making, the clinician and patient must have both the cognitive and communicative capacity to do so.[5] If the clinician has unfavorable attitudes or biases toward the patient or a noncritical belief in the value of certain treatments, his cognitive capacity may be diminished. The same can be said if he is complacent about clinical indicators and patient clues or if he does not consider the effect of his own beliefs and values. A patient's cognitive capacity may be limited by low health literacy or numeracy, if the clinical information she receives is not appropriately targeted, if she is unwilling or unable to participate in the discussion with an open mind, or if she is unable to process the information because of diabetes-related distress, as was the case with Jenny when she was diagnosed with T2DM.

Communicative capacity stems from the clinician's ability to engage in patient-centered communication: (1) attempting to elicit, understand, and validate the patient's perspective; (2) involving the patient in care and decision making to the extent desired by the patient; (3) providing clear, understandable explanations; and (4) fostering a relationship characterized by trust and commitment.[5] As shown in **TABLE 1,** both verbal and nonverbal clinician behaviors are associated with effective collaborative decision making that contributes to patient satisfaction, treatment implementation and sustainability, and improved health outcomes.[10] Strategies that can enhance shared decision making regarding the use of injectable glucose-lowering agents are outlined in **TABLE 2.** Not all patients will wish to engage in decision making at this level. Some may want to be actively involved in certain aspects, such as the dietary approach, but not in others, such as medication selection.

### Establishing an agenda

Establishing an agenda at the beginning of the office visit is an important element of collaborative decision making. One approach is to begin the visit by telling the patient that you

**TABLE 1 Examples of desirable communication behaviors[10]**

| | |
|---|---|
| **Nonverbal** | • Maintaining eye contact<br>• Leaning forward to indicate attentiveness<br>• Nodding to indicate understanding<br>• Absence of distracting movements (eg, fidgeting) |
| **Verbal** | • Establishing purpose of the visit<br>• Encouraging patient participation<br>• Avoiding interruptions<br>• Soliciting the patient's beliefs, values, and preferences<br>• Eliciting and validating the patient's emotions<br>• Asking about family and social context<br>• Providing sufficient information<br>• Providing clear, jargon-free explanations<br>• Checking for patient understanding<br>• Offering reassurance<br>• Offering encouragement and support |

**TABLE 2** **A collaborative approach to decision making for medications**

| | |
|---|---|
| **Assessing patient concerns** | Have you heard of or read about this medication? |
| | What worries you most about this medication? |
| | How do you think this medication will help you? |
| | What do you think will happen if things stay the same? |
| | How easily will taking this medication fit into your schedule? |
| | What might get in your way of taking this medication? |
| | Is there anything that would help you to be more faithful in taking this medication? |
| | What are your thoughts about taking an injection? What do you think will be hardest for you? What do you need to know to consider an injection? |
| | What other questions do you have? |
| | Is there anything else you need to know? |
| | On a scale of 1 to 10, how important do you think this medication is for you? |
| | On a scale of 1 to 10, how confident do you feel that you will be able to take this medication? |
| **Providing information** | What we know from the most recent studies is… |
| | Here is what is proven to work best… |
| | This is what the data show… |
| | Here is what my other patients have told me… |
| | I feel this medication is a good choice for you because… |
| | The most common side effects are… |
| | This is about how long this medication takes to start working… |
| | We will start with a low dose then increase it, so be patient… |
| | Let me show you how to administer this medication… |
| | Here are the costs and what your insurance will cover… |
| | Here are strategies for safety and to get the greatest benefit from this medication… |
| | This is how we can monitor your treatment plan… |
| | This is what I recommend for a follow-up plan… |
| | This is when you should call with problems… |

have things you need to accomplish during the visit, but that first you want to hear from the patient about how things have been going, what has been hardest for them since the last visit, and what they want to accomplish today. A form that can be completed by the patient in the waiting room, such as the Diabetes Concerns Assessment Form developed at the University of Michigan Diabetes Research and Training Center, may help to facilitate the discussion.[11] This form can be found at http://www.med.umich.edu/mdrtc/profs/documents/emh/ConcernsAssessment.pdf.

## CASE STUDY (CONTINUED)

In preparation for redesigning his practice to create a patient-centered medical home, Jenny's PCP asked her to complete a Concerns Assessment Form while she was waiting for her follow-up visit. Her PCP began the visit by reviewing Jenny's concerns with her.

***Jenny's concerns:***

- FBG hasn't improved as much as she hoped
- Weight gain of 1 kg
- Frequency of blood glucose monitoring
- Mild diarrhea (although it has subsided)
- Limited time to exercise

***PCP agenda:***

- Fatigue/energy level
- Blood glucose log
- Insulin dose, further titration
- Side effects, possibility of hypoglycemia

Establishing an agenda enables the clinician to address the patient's most pressing needs, with remaining issues deferred until a subsequent visit. Letting the patient know at the beginning of the visit that you have some agenda items

to address gives you the opportunity to end the discussion if needed due to time constraints. Although seemingly counter-intuitive, meeting the patient's agenda first has been shown to shorten the office visit by more than 10% (from 20.1 minutes to 17.6 minutes).[12] Additional benefits include an improved clinician–patient interaction from the patient's perspective. From the clinician's perspective, this approach enables the clinician to feel more in control, experience greater satisfaction with patient encounters, and feel less rushed. It is possible that office visits may take longer initially, but this approach saves time in the long run.[13]

### Communication

There is clear evidence that patients who have more collaborative and positive relationships with their clinicians report better health outcomes, less diabetes-related distress, and better overall self-management.[14-16] In addition to agenda setting, communication can be facilitated by using the "ask, listen, empathize" method of communication: (1) *ask* the patient to briefly expand on each of her agenda items or concerns; (2) *listen* to the patient's response without offering opinions, judgments, or advice; and (3) *empathize* and ask additional questions to promote discussion about the patient's thoughts and worries.[2] Active listening is essential because patients may disengage from the visit if the clinician dominates the discussion or if they are made to feel that they are not understood, have failed, or are a "bad patient." Empathizing allows clinicians to acknowledge their patients' distress and struggles and to show that they care about their patients and not just their weights, blood glucose levels, and other outcome measures.

#### CASE STUDY (CONTINUED)

While reviewing Jenny's blood glucose log, the PCP observes that her FBG levels range from 126 to 146 mg/dL, with 3 episodes of FBG between 160 to 170 mg/dL. He asks Jenny if she feels less overwhelmed and if she has experienced any difficulties. Jenny replies that she is doing better emotionally, but that she expected to have more energy by now. She also says that she has forgotten to take her insulin or check her blood glucose 4 or 5 times because her family life has been particularly demanding recently. Jenny expresses some frustration regarding the amount of effort it takes to manage diabetes and wonders if it is worth it if she is not going to feel better. Jenny also states that, while she has some concern about hypoglycemia, she is more upset about her weight gain.

### Goal setting

In Jenny's case, she has not experienced as much improvement as she anticipated, although her FBG levels are much improved and she is doing her best to manage her T2DM. Her concerns about weight gain and slow progress need to be acknowledged. A key step to support Jenny is to inform her that there are things she can do to prevent additional weight gain as her glucose levels normalize. Using the 5-step goal-setting model shown in **TABLE 3** can help Jenny to more clearly define the problems she is experiencing, identify how her emotions are influencing her behavior, set achievable goals, and create a behavior change plan to reach those goals.[2] The first 2 steps serve to identify a problem and determine the patient's beliefs, thoughts, and feelings that may support or impede self-management efforts. The third and fourth steps help to establish the long-term goals patients would like to achieve and the short-term actions needed to achieve those goals. Patients are then encouraged to take the action steps they identified, evaluate their effectiveness, and discover what was learned in the process. The lessons learned can be used either to revise the plan or create a new one.

One way for patients to articulate specific action steps is with the **I-SMART** mnemonic.[17] The behaviors they choose to address and the steps they take to achieve their goals need to be **I**nspiring and **I**mportant, **S**pecific, **M**easurable, **A**chievable, **R**elevant, and **T**imely.[17] Helping patients create their own action plans transfers responsibility for the success or failure of the plan from the clinician to the patient.

### Closing the loop

Once the agendas of both the patient and the provider have been addressed and items for future visits identified, it is time to "close the loop." The visit should be concluded by asking the patient to summarize in his or her own words what was discussed and what actions he or she will take as a result. This has been called a "teach back" technique (http://www.teachbacktraining.com). Although recall and comprehension of new concepts presented to patients during an office visit has been reported to occur in only 20% of patient encounters, this strategy has been shown to improve $HbA_{1c}$ levels.[18]

#### CASE STUDY (CONTINUED)

Jenny identifies that they have discussed and decided:

- Check her bedtime and FBG levels on Sunday, Monday, Wednesday, Friday
- Keep her insulin pen by her bed so she remembers to take her insulin
- Continue to work with the diabetes educator
- Meet with a nutritionist to address her continuing concerns about diabetes and weight gain
- Contact one of the PCP's patients who is willing to serve as a mentor

  -Alternatively, attend (with spouse if she wishes) a

**TABLE 3** Behavior change protocol[2]

| | |
|---|---|
| **Step 1: Explore the problem or issue (past)** | What is the hardest thing about caring for your diabetes?<br>Please tell me more about that.<br>Are there some specific examples you can give me? |
| **Step 2: Clarify feelings and their meaning (present)** | What are your thoughts about this?<br>Are you feeling [insert feeling] because [insert meaning]? |
| **Step 3: Develop a plan (future)** | What do you want?<br>How would this situation have to change for you to feel better about it?<br>Where would you like to be regarding this situation in [specific time, eg, 1 month, 3 months, 1 year]?<br>What are your options?<br>What are barriers for you?<br>Who could help you?<br>What are the costs and benefits for each of your choices?<br>What would happen if you do not do anything about it?<br>How important is it, on a scale of 1 to 10, for you to do something about this?<br>Let's develop a plan. |
| **Step 4: Commit to action (future)** | Are you willing to do what you need to do to solve this problem?<br>What are some steps you could take?<br>What are you going to do?<br>When are you going to do it?<br>How will you know if you have succeeded?<br>What is one thing you will do when you leave here today? |
| **Step 5: Experience and evaluate the plan (future)** | How did it go?<br>What did you learn?<br>What barriers did you encounter?<br>What, if anything, would you do differently next time?<br>What will you do when you leave here today? |

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group medical visit (see *Preparing for Success: Redesigning the Diabetes Office Practice* in this supplement)
- Increase metformin to 1000 mg twice daily
- Continue titration of insulin detemir to maximum of 35 U at dinner

## Additional resources

Numerous resources are available to guide the clinician in redesigning the clinician–patient office visit. Some of those resources are listed here.

- Family Practice Management: Four Strategies for Promoting Healthy Lifestyles in Your Practice: http://www.aafp.org/fpm/2011/0300/p16.html
- California Healthcare Foundation: Self-Management Support Training Materials: http://www.chcf.org/publications/2009/09/selfmanagement-support-training-materials
- American Diabetes Association: Personalizing Patient Goals and Care in Type 2 Diabetes: One Size Does Not Fit All: http://www.idoc.org/ada/intro
- Behavioral Diabetes Institute: Introduction to Motivational Interviewing: Simple Strategies for Promoting Positive Behavior Change in Diabetes: http://www.behavioraldiabetesinstitute.org/resources-diabetes-information-videos-BDI-lectures.html
- American Diabetes Association: Conversation Maps™: http://www.diabetesincontrol.com/issues/Issue_317/about_healthyi.pdf


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# Preparing for Success: Redesigning the Diabetes Office Practice

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DISCLOSURES
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## INTRODUCTION

Diabetes is a demanding chronic illness that challenges every aspect of a patient's body, mind, and spirit and requires a complete reorientation of a patient's life. Multiple medications, needle sticks, food restrictions, exercise, and frequent visits to health care providers are some of the challenges faced by patients with diabetes. An additional challenge is the incorporation of these changes into a lifestyle that is strongly influenced by culture, belief system, values, socioeconomics, family, religion, and psychosocial well-being. Evidence exists to show that reaching evidence-based goals for glycosylated hemoglobin ($HbA_{1C}$), low-density lipoprotein cholesterol, and blood pressure significantly reduces the complications and cost of diabetes.[1-3]

While effective therapeutic options are available for reaching these goals, even with our best efforts, only about one-third to one-half of patients are able to reach any of these goals individually[4-7] and only 19% of patients with diabetes reach all 3 at the same time.[7] Difficulty with reaching these goals creates frustration and distress, most of all for the patient but also for the diabetes care team, which includes the physician, nurse, pharmacist, and certified diabetes educator.[8] To better improve the health outcomes of patients with type 2 diabetes mellitus (T2DM), evolving practice guidelines have increasingly recommended a more aggressive management approach that includes the earlier use of injectable glucose-lowering agents, specifically insulin and the glucagon-like peptide-1 receptor (GLP-1R) agonists.[9,10]

To effectively manage patients with T2DM, it is necessary to recognize that diabetes is a mostly self-managed disease,[11] with short- and long-term health outcomes largely determined by the patient. Consequently, the role of the health care team in managing patients with a chronic disease such as diabetes is different than managing a patient with an acute illness. In providing care to a patient with diabetes, the clinician and other team members serve as coaches who provide information and support within a system of care that ministers not only to the medical needs of the patient, but to the biological, social, and psychological needs as well. Providing this diverse support often requires a redesign of not only the patient visit (see *Engaging the Patient in Diabetes Self-Management* in this supplement) but also the medical practice into a "participatory office practice" as described below.

This article addresses many of the issues related to designing a participatory office practice to provide effective care for patients with T2DM once the decision has been made to utilize injectable glucose-lowering therapy. Injectable glucose-lowering therapies are the focus of this article since most primary care physicians are less familiar with injectable medications, yet despite the higher medication costs for most patients, the use of injectable medications to treat patients with diabetes and other diseases is increasingly common. Also included in this article are discussions of the Plan-Do-Study-Act (PDSA) cycle (a component of the Model for Improvement), value-based health care (VBHC), and accountable care, as they relate to diabetes care.

### Redesigning the office practice

The manner in which many health care systems and practices are currently designed can make it difficult for primary care providers to fully support the needs of patients

treated with injectable glucose-lowering therapy and to deliver all of the elements of comprehensive diabetes care recommended by the American Diabetes Association and the American Association of Clinical Endocrinologists.[10,12] To address these design shortcomings, several models for care delivery have been proposed, including the chronic care model,[13] the medical home model,[14] and the healthy learner model.[15] Each of these models emphasizes the patient as the focus of care and includes his or her active participation in decision making.

Fostering patient self-management, which is a critical component of these models, can be more challenging with insulin or GLP-1R agonists than with other glucose-lowering agents due to the need to use a device for administration and the perception that their use is complex and injections are painful. In addition, concerns commonly associated with insulin, such as the need for frequent titration and blood glucose monitoring, injection pain, hypoglycemia, and weight gain, may serve as barriers to treatment and contribute to psychological distress.[16-18] To support the patient in overcoming these concerns and in learning and acquiring the necessary skills for self-management, the ongoing involvement of an expanded health care team is essential. The team consists of the physician, nurse, pharmacist, diabetes educator, social worker, case manager, medical assistant, podiatrist, dentist, ophthalmologist, and possibly others with complementary skills. Family members may also be included as part of the team and should be included in patient education, particularly those who provide care to a child or an older adult.

## Developing a participatory office practice

The participatory office practice makes patient-focused care operational within a system of care. To support the diverse needs of a patient with T2DM, this system of care includes a multidisciplinary health care team.[19] Acting under the leadership of the physician, team members must work collaboratively toward shared goals with similar approaches. While this may sound simple, the rapidly evolving nature of T2DM management can make this challenging. Frequent meetings between the health care professional team members, wherein education and experiences are shared and problems are identified and solved collaboratively, can be effective in keeping the team functioning properly. Team members should also share and discuss evolving news and US Food and Drug Administration actions related to diabetes medications and devices so that they are better able to provide consistent responses to patient questions.

The National Diabetes Education Program (NDEP) identified 6 team-building steps that are important for creating or expanding team care.[20] These steps are: (1) ensure the commitment of leadership; (2) identify team members; (3) identify the patient population; (4) assess resources; (5) develop a system for coordinated, continuous, high-quality care; and (6) evaluate outcomes and adjust as necessary. One approach to evaluate outcomes and adjust as necessary is the PDSA cycle described below.

The NDEP outlined 5 activities to maintain a successful team regardless of structure and purpose: (1) promote patient satisfaction, quality of life, and self-management; (2) promote a community support network; (3) maintain team coordination and communication; (4) provide ongoing patient follow-up; and (5) use health information technology. Case examples of successful diabetes care teams in diverse settings are described in *Redesigning the Health Care Team: Diabetes Prevention and Lifelong Management,* available at http://www.ndep.nih.gov/media/ndep37_redesignteamcare_4c_508.pdf). Additional resources for practice redesign are also available from the NDEP (http://www.ndep.nih.gov/hcp-businesses-and-schools).

## What tools are needed to develop a participatory office practice?

Any function provided by a nonphysician member of the health care team should be supported, at a minimum, by the same tool(s) used by the physician if he or she were providing the function. Some of these functions include screening for diabetes distress; identifying patient barriers to effective diabetes care (eg, loss of insurance coverage, transportation difficulties, low numeracy or literacy); and ensuring patient follow through with other appointments (eg, eye or foot examinations, dental care, and laboratory tests), prescription refills, and annual influenza vaccinations. An example of a tool used to screen for diabetes stress is the Diabetes Distress Scale.[8] Patient completion of the Diabetes Distress Scale can be facilitated and reviewed by a nonphysician member of the patient's care team.

Gaps in care can be identified with a diabetes registry. The registry can be used by a team member to track the patient's diabetes-related parameters and other activities (**TABLE 1**).[21] The registry can also be used to track completion of other parameters, such as periodic validation of a patient's self-injection technique, participation in diabetes educational programs offered by the primary care physician or others, or periodic completion of the Diabetes Distress Scale. Registry functions are increasingly available in electronic medical record software. If the registry shows that the patient has not had a recommended laboratory test, vaccination, or eye, foot, or dental examination, the team member can order the test or arrange for a referral, following an approved protocol. Similarly, steps can be taken to address other parameters if they are not completed.

**TABLE 1** **The patient report card from a diabetes registry**

| | GOAL | | DATE | DATE | DATE |
|---|---|---|---|---|---|
| Weight | | | | | |
| Blood pressure | <140/80 mm Hg (best if <130/80 mm Hg)[a] | | | | |
| **TESTS** | | | | | |
| $HbA_{1c}$ (blood sugar over past 3 months) | <7.0%[a] (best if <6.0%) | | | | |
| LDL-cholesterol (lousy cholesterol) | <100 mg/dL (best if <70 mg/dL)[a] | | | | |
| HDL-cholesterol (happy cholesterol) | >40 mg/dL (men); >50 mg/dL (women)[a] | | | | |
| Triglycerides (a bad, fatty substance) | <150 mg/dL[a] | | | | |
| **MEDICATION(S)** | **DIRECTIONS** | | | | |
| Aspirin - low dose | Take daily | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| **IMPORTANT YEARLY ACTIVITIES** | **GOAL** | **STATUS** | **NEXT TEST DUE** | **MOST RECENT TEST** | **PREVIOUS TEST** |
| Eye examination (to prevent blindness) | 1 time a year | | | | |
| Foot examination (to check for sores and numbness) | 1 time a year | | | | |
| Urine microalbumin (to check for kidney failure) | 1 time a year | | | | |
| Flu shot (to prevent influenza) | 1 time a year | | | | |
| Pneumococcal vaccine (to prevent special pneumonia) | Once in lifetime (2 times if first given before age 65 years) | | | | |
| Smoking (dangerous to your health; increases complications of diabetes) | Please stop smoking | | | | |

[a]As defined by the American Diabetes Association

Abbreviations: $HbA_{1c}$, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.



Empowering nonphysician team members to perform appropriately delegated functions enables the physician to work more efficiently and to focus on issues requiring a physician's specialized skills. The team care model also promotes optimal patient care, may improve satisfaction among other health care professionals, and may lead to cost reduction. Another benefit of empowering nonphysician team members is that patients themselves may feel more empowered and engaged in their self-management.

Group medical visits provide another tool to be used to more fully engage the patient in his or her self-management. Group visits are an innovative way to help patients with diabetes (or other chronic diseases) better self-manage by allowing them to share their experiences with and learn from other patients. Changes in patient behavior are more likely to occur through this exchange of personal experiences and the emotions that accompany them, rather than as a result of more traditional educational processes (eg, lectures).

Preliminary results of a survey being conducted through TransforMed, an initiative founded by the American Academy of Family Physicians to transform health care delivery to achieve optimal patient care, professional satisfaction, and the success of primary care practices, show that both providers and patients see the group medical visit as beneficial and as a good means for providing patient education (unpublished results). Unlike group education classes or support groups, group medical visits provide support for self-management skills as well as medical evaluations, changes in treatment plans, care coordination, and preventive services.

**TABLE 2** Possible targets for improvement related to injectable glucose-lowering therapy

| What are we trying to accomplish? | How will we know that a change is an improvement? | What changes can we make that will result in improvement? |
|---|---|---|
| Improve glycemic control | • Lower $HbA_{1c}$ (patient)<br>• More patients in practice achieve glycemic target | • Adopt ADA/EASD or AACE algorithm<br>• Intensify treatment if $HbA_{1c}$ above target for more than 3 months |
| Reduce incidence of hypoglycemia | • Reduced emergency department visits<br>• Reduced FBG levels <70 mg/dL on BG log | • Implement written action plan<br>• Provide family education<br>• Assess patients for hypoglycemia unawareness<br>• Minimize utilization of glucose-lowering therapy most likely to cause hypoglycemia |
| Reduce treatment-related weight gain | • Decrease in patient weight, BMI | • Nutrition referral<br>• Increase utilization of glucose-lowering therapy that promotes weight loss (GLP-1R agonists, SGLT-2 inhibitor) or is weight neutral (metformin, DPP-4 inhibitor, AGI, colesevelam, bromocriptine) |

Abbreviations: AACE, American Association of Clinical Endocrinologists; ADA/EASD, American Diabetes Association/European Association for the Study of Diabetes; AGI, alpha-glucosidase inhibitor; BG, blood glucose; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; $HbA_{1c}$, glycosylated hemoglobin; SGLT-2, sodium-glucose cotransporter-2.

Group visits can be especially helpful when patients with T2DM share a common experience or challenge. For example, a group meeting of patients who self-manage with injectable glucose-lowering therapy can be an effective educational format by enabling patients to share their experiences and how they addressed their medical and psychosocial challenges related to injectables. The group meeting works particularly well when there is a mix of experience among the participants. Group meetings can also be helpful to those contemplating initiation of an injectable agent because it enables them to learn about the experiences of others.

A key strategy for team members who participate in the group visit is to let patients lead the visit. For example, rather than beginning a group visit by giving a lecture or providing information, team members might start by asking patients to share experiences or ask questions. While in essence, the patients are encouraged to establish the agenda, it is important for team members to identify the topic for discussion prior to the group visit. Further information and resources about group visits can be found through TransforMed (http://www.transformed.com/resources/groupVisits.cfm) and the Diabetes Master Clinician Program (http://www.diabetesmasterclinicians.org/group-visits.html).

## What is the Plan-Do-Study-Act cycle and how is it relevant for caring for patients with diabetes?

The PDSA cycle is 1 of the 2 components of the Model for Improvement—a tool for accelerating outcome improvement that has been widely used within health care.[22] The first component of this model asks 3 fundamental questions: (1) What are we trying to accomplish? (2) How will we know that a change is an improvement? and (3) What changes can we make that will result in improvement? The first question requires setting goals that are time-specific and measurable. The goals should also define the specific population of patients (eg, patients with T2DM) or the system that will be affected (eg, laboratory monitoring, patient education). The second question establishes quantitative measures to determine if a specific change actually leads to an improvement. Parameters for the third question may come from various sources, such as change concepts, the experience of other providers or researchers, people who provide patient care, or people who work within the system that will be affected. Possible targets for improvement related to injectable glucose-lowering therapy are listed in **TABLE 2**.

The PDSA cycle is then used to test the results of the change being evaluated (**TABLE 3**). By making a change and reflecting on the consequences of that change, repeated flow through the cycle leads to increased knowledge and improvement in the identified aspect of patient care. A key to successful implementation of the PDSA cycle is to embed the process into daily practice so that it is seamless. Particularly when first implementing the cycle, it is suggested that the change be small in scope.

## What is value-based health care?

Value-based health care focuses on costs, quality, and outcomes across a defined population rather than for an individ-

**TABLE 3** Plan-Do-Study-Act cycle of quality improvement[22]

| | |
|---|---|
| **Plan** | • Describe the change<br>• Predict the outcome<br>• List tasks needed<br>• Plan for collection of data |
| **Do** | • Implement on a small scale and see plan to completion<br>• Document any unforeseen problems or other unexpected observations |
| **Study** | • Review and analyze the data and compare them to the predicted results<br>• Summarize and reflect on what was learned from performing the cycle |
| **Act** | • Choose to adopt the change, abandon it, or make changes; run the cycle again under different environmental conditions |

ual patient.[23] The goal of VBHC is to remove barriers to good health and encourage participants within a specific organization to pursue healthy lifestyles. For example, participants may continue poor nutrition or physical activity habits, despite knowing that such habits may contribute to diabetes, if they feel that adopting good habits would diminish their enjoyment of life. The expectation is that these strategies to pursue a healthy lifestyle will result in a healthy workforce. Using VBHC to pursue high-quality, high-value health care, thereby reducing the need for high-cost medical services, requires collaboration among organization sponsors, health plan participants, and health care providers.

Value-based health care is the values counterpart to evidence-based medicine (EBM). Whereas EBM pertains to the best available clinical evidence, VBHC relates to the diversity of values among health care providers and patients, as well as to the issue of who makes the final decisions about care.[24] Both are important in clinical decision making.[25] For example, while there is good evidence that lifestyle management plays an important part in T2DM management, some patients may elect to not modify their lifestyle, instead placing a higher value on their current lifestyle than on the desirable consequences that may result from modifications (eg, more energy, improved glycemic control, reduced need for medication).

Diabetes registries can aid in improvements related to VBHC. For example, the registry could be used to identify patients not at their $HbA_{1c}$ goal, despite maximally tolerated doses of dual-agent therapy. Actions that could be taken include identifying those with a history of poor adherence, determining the factors contributing to poor adherence, and implementing appropriate interventions. Another example would be identifying the agents used for dual therapy by patients and, if found to be inconsistent with current evidence, modifying the use of those agents based on patient characteristics.

### What is meant by accountable care?

Accountable care strives to provide: (1) better care and health outcomes; (2) access to the right care and to a better patient experience; and (3) lower cost.[26] Essentially, accountable care is value-based, data-driven, patient-centered care that rewards quality of care over quantity of care. With accountable care, payment for care is linked to the outcomes of care and aligns payment with improved efficiency and effectiveness in managing the care of a defined group of patients. The goal is for health care providers, payers, and patients to collaborate to produce proactive, preventive health care that improves patient outcomes while maximizing the value of the services provided. Regarding patients with T2DM, an accountable care organization (ACO) might seek to improve patient outcomes and reduce costs by focusing on hospital admissions and readmissions for diabetes-related events, such as hypoglycemia. For example, for patients being treated with a drug associated with a high risk of hypoglycemia, switching to an agent with a low risk could be undertaken. An ACO might also identify patients not at glycemic goal; determine the patient, provider, and system factors responsible; and implement interventions using the PDSA cycle.

An ACO is a group of primary care providers, specialists, and hospitals that voluntarily collaborate and collectively accept accountability for the cost and quality of care delivered to a population of patients.[27,28] Like the patient-centered medical home, the ACO is based on strong primary care services. ACOs include many medical homes that work together and, in fact, some have called ACOs the medical neighborhood. A difference between the patient-centered medical home and an ACO is that the latter is accountable for the cost and quality of care both within and outside of the primary care relationship. Thus an ACO must include specialists and hospitals to be able to control costs and improve health outcomes across the entire continuum of care.[27] It is believed that ACOs can achieve both cost and quality improvements because the coordinated and collaborative nature of the delivery system is rewarded for its outcomes, not for its volume of services.

## SUMMARY

Improving health outcomes of patients with T2DM whose management includes injectable glucose-lowering therapy may require a redesign of the diabetes office practice to support patients' medical and psychosocial needs. This redesign may include the development of a participatory office practice wherein care is provided by a multidisciplinary diabetes

care team. To make stepwise improvements in any facet of patient care, the PDSA cycle can be integrated into routine clinical practice. Value-based health care and accountable care are evolving approaches intended to improve patient outcomes.


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