CLINICAL GUIDELINE

Annals of Internal Medicine

Pharmacologic Therapy for Type 2 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes

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Description: The American Diabetes Association (ADA) annually updates the Standards of Medical Care in Diabetes to provide clinicians, patients, researchers, payers, and other interested parties with evidence-based recommendations for the diagnosis and management of patients with diabetes.

Methods: For the 2017 Standards, the ADA Professional Practice Committee updated previous MEDLINE searches performed from 1 January 2016 to November 2016 to add, clarify, or revise recommendations based on new evidence. The committee rates the recommendations as A, B, or C, depending on the quality of evidence, or E for expert consensus or clinical experience. The Standards were reviewed and approved by the Executive Committee of the ADA Board of Directors, which includes health care professionals, scientists, and laypersons. Feedback from the larger clinical community informed revisions.

Recommendations: This synopsis focuses on recommendations from the 2017 Standards about pharmacologic approaches to glycemic treatment of type 2 diabetes.

Ann Intern Med. 2017;166:572-578. doi:10.7326/M16-2937 **Annals.org**
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This article was published at Annals.org on 14 March 2017.

The American Diabetes Association (ADA) first released its Standards of Medical Care in Diabetes for health professionals in 1989. These practice guidelines provide an extensive set of evidence-based recommendations that are updated annually for the diagnosis and management of patients with diabetes. The 2017 Standards cover all aspects of patient care (1); this guideline synopsis focuses on pharmacologic approaches for patients with type 2 diabetes.

Guideline Development and Evidence Grading

To develop the 2017 Standards, the ADA Professional Practice Committee, which comprises physicians, adult and pediatric endocrinologists, diabetes educators, registered dietitians, epidemiologists, and public health experts, systematically searched MEDLINE from 1 January 2016 (date of last previous search) to November 2016. The committee revised recommendations based on the new evidence or, in some cases, to clarify prior ones or match the strength of the wording to the strength of the evidence. It also solicited feedback from the larger clinical community.

The recommendations are rated as A, B, C, or E. Those with an A rating are based on large, well-designed, multicenter clinical trials or high-quality meta-analyses. Recommendations with lower-quality evidence may be equally important and are based on well-conducted cohort studies (B rating) or uncontrolled studies (C rating). Those assigned an E rating are consensus recommendations for which there is no evidence from clinical trials, in which clinical trials may be impractical, or in which there is conflicting evidence.

The ADA funds development of the Standards from its general revenues with no industry support or involvement. Details on the methodology, information about the committee members and their conflict-of-interest disclosures, and the complete Standards can be downloaded at professional.diabetes.org/annals.

See also:

Web-Only
CME/MOC activity

Pharmacologic Therapy for Type 2 Diabetes: Recommendations

Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes (A rating). Long-term use of metformin may be associated with biochemical vitamin B_{12} deficiency, and periodic measurement of vitamin B_{12} levels should be considered in patients treated with metformin, especially those with anemia or peripheral neuropathy (B rating). Providers should consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic, have a hemoglobin A_{1c} (HbA_{1c}) level of 10% or greater, or have a blood glucose level of 16.7 mmol/L (300 mg/dL) or greater (E rating). If noninsulin monotherapy at the maximum tolerated dose does not achieve or maintain the HbA_{1c} target after 3 months, adding a second oral agent, a glucagon-like peptide-1 (GLP-1)–receptor agonist, or basal insulin should be considered (A rating). For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should be instituted without delay (B rating). A patient-centered approach should be used to guide the choice of pharmacologic agents (E rating).

Initial Treatment Approach: Metformin

Metformin monotherapy should be initiated at the time of diagnosis of type 2 diabetes for most patients

Table 1. Median Monthly Cost of Maximum Approved Daily Dose of Noninsulin Glucose-Lowering Agents in the United States*

Class	Compound	Dosage Strength/Product (If Applicable)	Median AWP (Range), $†	Maximum Approved Daily Dose‡
Biguanides	Metformin	500 mg (IR)	84 (5–94)	2000 mg
		850 mg (IR)	108 (5–108)	2550 mg
		1000 mg (IR)	86 (4–87)	2000 mg
		500 mg (ER)	90 (82–6672)	2000 mg
		750 mg (ER)	72 (65–92)	1500 mg
		1000 mg (ER)	1028 (1010–7213)	2000 mg
Sulfonylureas (second generation)	Glyburide	5 mg	94 (64–103)	20 mg
		6 mg (micronized)	50 (48–71)	12 mg (micronized)
	Glipizide	10 mg (IR)	74 (67–97)	40 mg (IR)
		10 mg (XL)	97	20 mg (XL)
	Glimepiride	4 mg	74 (71–198)	8 mg
Meglitinides (glinides)	Repaglinide	2 mg	799 (163–878)	16 mg
	Nateglinide	120 mg	156	360 mg
Thiazolidinediones	Pioglitazone	45 mg	349 (348–349)	45 mg
	Rosiglitazone	4 mg	355	8 mg
α-Glucosidase inhibitors	Acarbose	100 mg	104 (104–105)	300 mg
	Miglitol	100 mg	241	300 mg
Dipeptidyl peptidase-4 inhibitors	Sitagliptin	100 mg	436	100 mg
	Saxagliptin	5 mg	436	5 mg
	Linagliptin	5 mg	428	5 mg
	Alogliptin	25 mg	436	25 mg
Bile acid sequestrant	Colesevelam	625 mg tabs	679	3.75 g
		1.875 g suspension	1357	3.75 g
Dopamine-2 agonists	Bromocriptine	0.8 mg	719	4.8 mg
Sodium–glucose cotransporter 2 inhibitors	Canagliflozin	300 mg	470	300 mg
	Dapagliflozin	10 mg	470	10 mg
	Empagliflozin	25 mg	470	25 mg
Glucagon-like peptide-1–receptor agonists	Exenatide	10 μg pen	729	20 mg
	Exenatide (ER)	2 mg powder for suspension or pen	692	2 mg§
	Liraglutide	18 mg per 3 μL pen	831	1.8 μg
	Albiglutide	50 mg pen	527	50 mg§
	Dulaglutide	1.5 mg per 0.5 mL pen	690	1.5 mg§
Amylin mimetics	Pramlintide	120 μg pen	2124	120 μg per injection‖

AWP = average wholesale price; ER = extended release; IR = immediate release; XL = extended release.
* Adapted from reference 9 and the American Diabetes Association.
† Calculated for 30-d supply (AWP unit price × number of doses required to provide maximum approved daily dose × 30 d); median AWP listed alone when only 1 product and/or price.
‡ Used to calculate median AWP (range); generic prices used if available commercially.
§ Administered once weekly.
‖ AWP calculated based on 120 μg 3 times daily.

unless there are contraindications. It is effective, safe, and inexpensive and may reduce the risk for cardiovascular events and death (2). A large meta-analysis (3) supports the use of metformin monotherapy as first-line therapy. It may be safely used in patients with an estimated glomerular filtration rate as low as 30 mL/min/1.73 m^2 (4); the U.S. label of metformin was recently revised to reflect its safety in patients with an estimated glomerular filtration rate of 30 mL/min/1.73 m^2 or greater (5).

Gastrointestinal side effects are common in patients receiving metformin. In the authors' experience, these side effects can be reduced if metformin monotherapy is started at a dose of 500 mg once or twice daily with food and titrated gradually to the maximum effective dose (2 g/d). Patients should be advised to stop taking their medication if they experience nausea, vomiting, or dehydration.

The Diabetes Prevention Program Outcomes Study found that long-term users of metformin may develop vitamin B_{12} deficiency. Periodic testing of vitamin B_{12} levels should be considered in metformin users, especially those with anemia or peripheral neuropathy (6).

USING PHARMACOTHERAPIES OTHER THAN OR IN ADDITION TO METFORMIN

If the patient does not tolerate or has a contraindication to metformin, another option should be considered. The ADA/European Association for the Study of Diabetes position statement (7) recommends a patient-centered approach, including assessment of efficacy, hypoglycemia risk, effect on weight, side effects, cost, and patient preferences. A table detailing characteristics of all available glucose-lowering agents in the United States that may guide individualized treatment choices is available in section 8 of the Standards (8). Tables 1 and 2 depict the costs of antihyperglycemic agents that were extracted from the *Red Book* (9). With so many choices, patients and providers should be able to find a mutually agreeable treatment option.

For patients with an HbA_{1c} level of 9% or greater who are not acutely symptomatic, initiation of dual combination therapy (Figure 1) should be considered to more quickly achieve the target HbA_{1c} level. If the patient has a random glucose level of 16.7 mmol/L (300 mg/dL) or greater or an HbA_{1c} level of 10% or greater and has acute symptoms of polyuria, polydipsia, or

Table 2. Median Cost of Insulins in the United States, Calculated as the AWP per 1000 Units of Specified Dosage Form/Product*

Compounds	Dosage Form/ Product	Median AWP Package Price (Range), $†
Rapid-acting analogues		
Lispro	U-100 vial	306
	U-100 3 mL cartridges	306 (306–379)
	U-100 prefilled pen; U-200 prefilled pen	394
Aspart	U-100 vial	306
	U-100 3 mL cartridges	380
	U-100 prefilled pen	395
Glulisine	U-100 vial	283
	U-100 prefilled pen	365
Inhaled insulin	Inhalation cartridges	557 (453–754)
Short-acting		
Human regular	U-100 vial	165
Intermediate-acting		
Human NPH	U-100 vial	165
	U-100 prefilled pen	350
Concentrated human regular insulin		
U-500 human regular insulin	U-500 vial	165
	U-500 prefilled pen	213
Basal analogues		
Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	298
Detemir	U-100 vial; U-100 prefilled pen	323
Degludec	U-100 prefilled pen; U-200 prefilled pen	355
Premixed products		
NPH/regular 70/30	U-100 vial	165
	U-100 prefilled pen	350
Lispro 50/50	U-100 vial	317
	U-100 prefilled pen	394
Lispro 75/25	U-100 vial	317
	U-100 prefilled pen	394
Aspart 70/30	U-100 vial	318
	U-100 prefilled pen	395

AWP = average wholesale price; NPH = neutral protamine Hagedorn.
* Adapted from reference 9 and the American Diabetes Association.
† AWP listed alone when only 1 product and/or price.

weight loss, combination therapy that includes insulin should be considered (Figure 2).

Assessing Response and Deciding to Intensify Therapy

Providers should assess whether the HbA_{1c} target has been achieved within approximately 3 months of therapy initiation (Figure 1); if it has not, therapy should be intensified (Figure 2). They should use shared decision making and a patient-centered approach when selecting a second agent. Potential combination therapies include a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium–glucose contransporter-2 (SGLT-2) inhibitor, GLP-1–receptor agonist, or basal insulin. Insulin should also be considered as part of any combination regimen for patients with severe hyperglycemia, especially if symptoms or catabolic features (such as weight loss or ketosis) are present. Patients should be reassessed within 3 months for achievement of the HbA_{1c} target.

Recent Evidence From Cardiovascular Outcomes Trials

Major cardiovascular outcomes trials have studied patients with type 2 diabetes and established cardiovascular disease, including EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) (10) and the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial (11). These 2 studies found that, compared with placebo and standard treatment, empagliflozin and liraglutide reduced composite outcomes for myocardial infarction, stroke, and cardiovascular death in populations in which most, if not all, patients had established atherosclerotic cardiovascular disease. Whether other agents in the same class as empagliflozin and liraglutide have similar benefits, and whether the treatments benefit patients at lower risk for cardiovascular disease, is unknown.

Cardiovascular outcomes trial data for the DPP-4 inhibitors sitagliptin (12), saxagliptin (13), and alogliptin (14) showed no statistically significant differences in rates of major cardiovascular events between treatment and placebo groups.

Recent Warnings About Pharmacotherapies

In May 2015, the U.S. Food and Drug Administration (FDA) issued a warning that SGLT-2 inhibitors may lead to ketoacidosis in the absence of significant hyperglycemia (termed "euglycemic diabetic ketoacidosis"). Patients who develop symptoms of ketoacidosis, which may include dyspnea, nausea, vomiting, and abdominal pain, should stop taking SGLT-2 inhibitors and immediately seek medical attention (15).

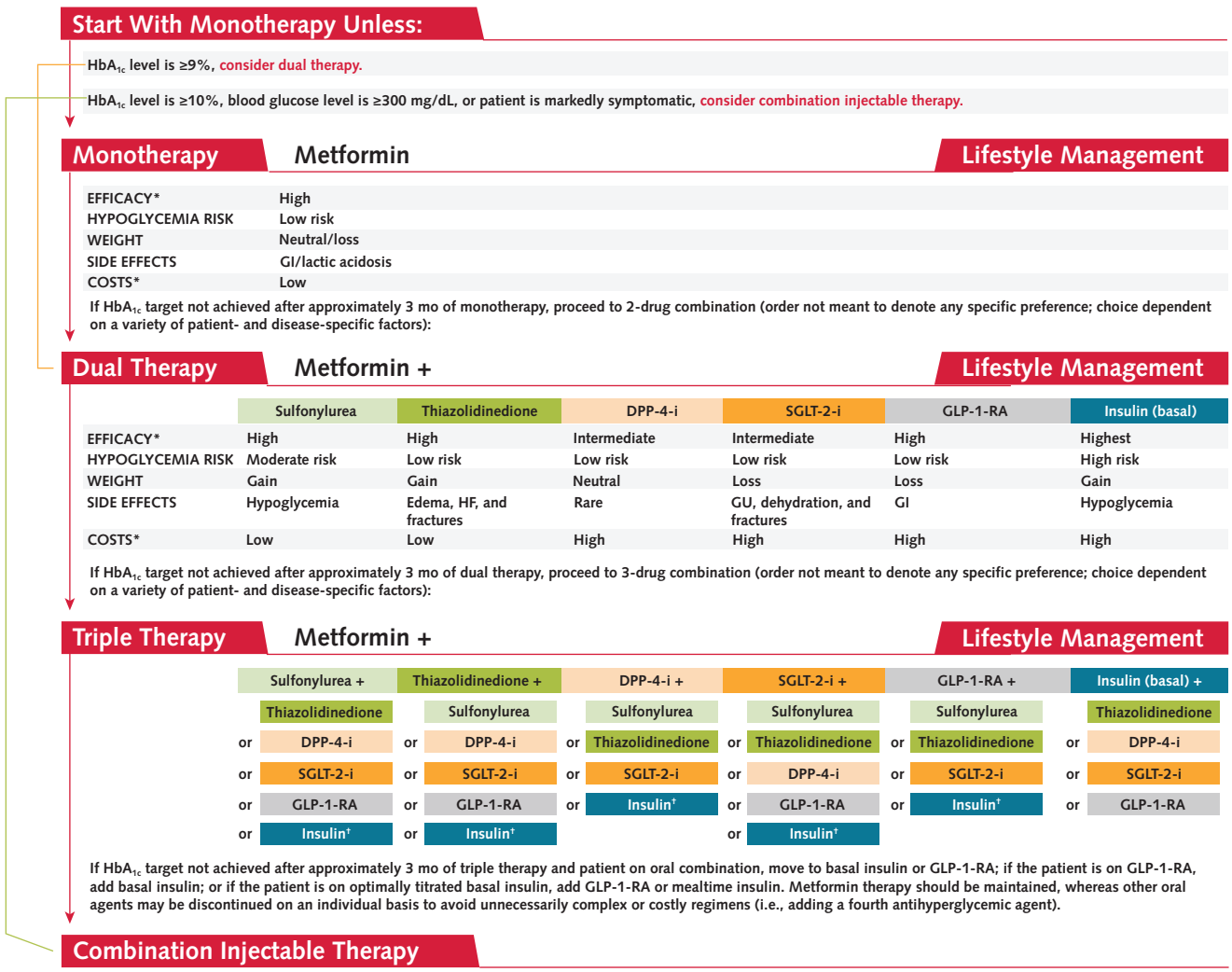
In April 2016, the FDA also warned that the DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients with preexisting heart failure or renal impairment (16).

Insulin Therapy

Diabetes is a progressive condition, and many patients with type 2 diabetes eventually require and benefit from insulin therapy. Early patient education about expected disease progression, and avoidance of threats of future insulin therapy (because it makes the expected transition more difficult), is important. Comprehensive education about blood glucose monitoring, nutrition, and hypoglycemia recognition and treatment are critical to patients receiving insulin therapy. Empowering patients with self-titration algorithms based on self-monitoring can improve glucose control in those with type 2 diabetes initiating insulin therapy (17).

A safe and simple approach is to prescribe 10 units, or 0.1 to 0.2 units/kg of body weight, of basal insulin per day and advise to increase the dose by 10% to 15%, or 2 to 4 units, once or twice weekly until the fasting blood glucose target is met. Insulin is typically

Figure 1. Antihyperglycemic therapy for type 2 diabetes: general recommendations.



The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). Adapted with permission from Inzucchi and colleagues (7). DPP-4-i = dipeptidyl peptidase-4 inhibitor; GI = gastrointestinal; GLP-1-RA = glucagon-like peptide-1–receptor agonist; GU = genitourinary; HbA_{1c} = hemoglobin A_{1c}; HF = heart failure; SGLT-2-i = sodium–glucose contransporter-2 inhibitor.

* See Dieuzeide and colleagues (21) for description of efficacy and cost categorizations.

† Usually a basal insulin (such as neutral protamine Hagedorn, glargine, detemir, or degludec).

used with metformin and sometimes 1 additional non-insulin agent. Cost considerations are important when an insulin product is selected, particularly because of substantial price increases over the past decade. Although newer products cause less hypoglycemia, intermediate-acting insulin (neutral protamine Hagedorn [NPH]) may be a more affordable option for some patients (18).

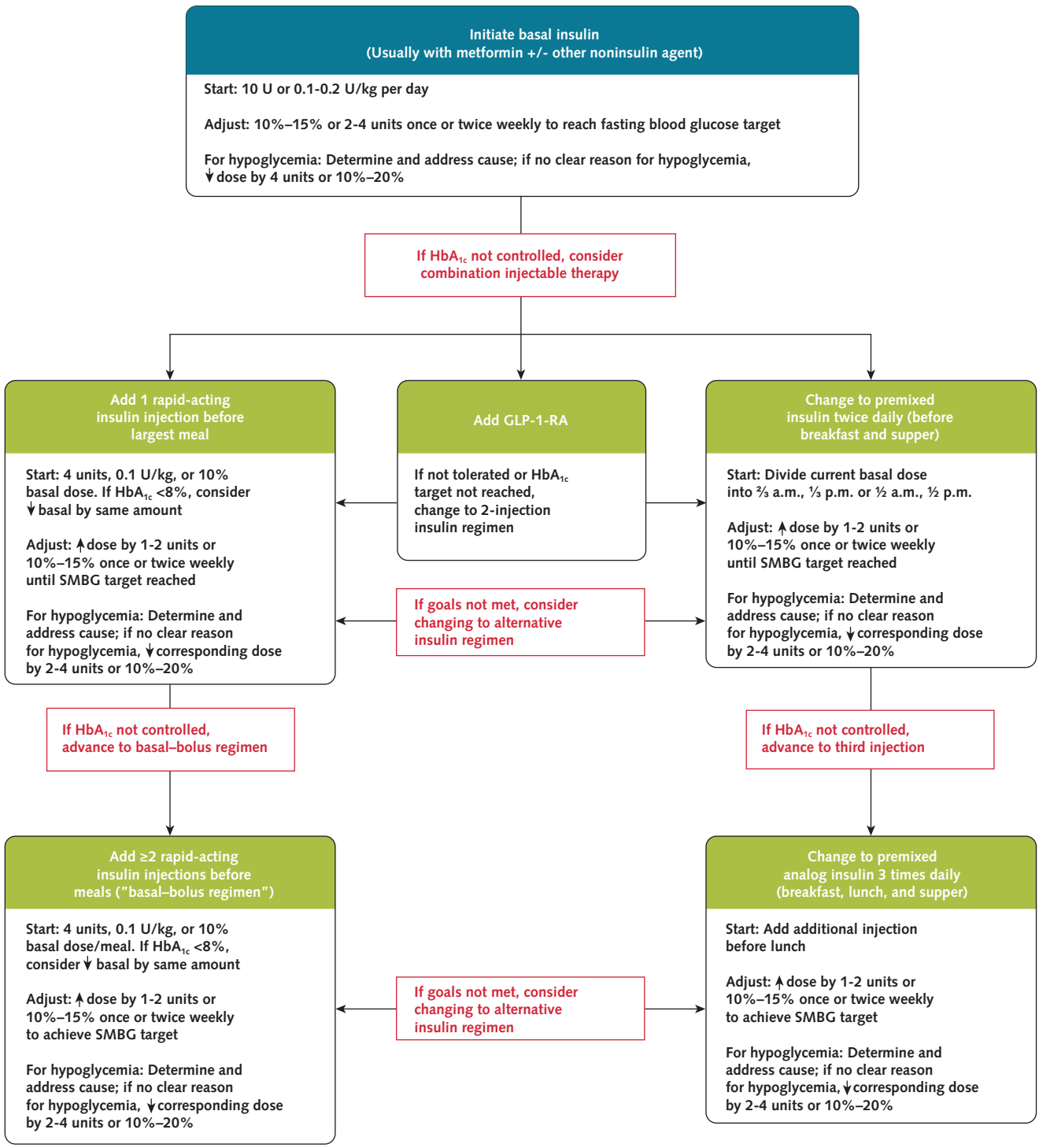
Advancing insulin therapy for patients not achieving HbA_{1c} goals on optimally titrated basal insulin alone often requires premeal insulin dosing. The rapid-acting insulin analogues are preferred because of their quick onset of action. The recommended starting dose of mealtime insulin is 4 U per meal, 0.1 U/kg per meal, or 10% of the basal insulin dose per meal if the HbA_{1c} level is less than 8%. Providers should consider decreasing the basal insulin dose by the same amount of the starting mealtime dose.

Premixed insulin products containing both basal and bolus insulin are another option for patients who may benefit from simpler dosing. These contain a fixed proportion of basal and prandial insulin to target both fasting and postprandial glycemia. The main disadvantage is that this approach requires a relatively fixed meal schedule and carbohydrate content per meal.

Concentrated Insulin Products

Several concentrated insulin preparations are available. The U-500 formulation of regular insulin is, by definition, 5 times as concentrated as the U-100 formula-

Figure 2. Combination injectable therapy for type 2 diabetes.



Adapted with permission from Inzucchi and colleagues (7). GLP-1-RA = glucagon-like peptide-1–receptor agonist; HbA_{1c} = hemoglobin A_{1c}; SMBG = self-monitored blood glucose.

tion. The former has a delayed onset and longer duration of action than the latter and has both prandial and basal properties. U-500 insulin is indicated for patients requiring more than 200 units of insulin per day. U-300 glargine and U-200 degludec have longer durations of action than their U-100 formulations, which allow for higher doses of basal insulin per volume. The FDA has also approved a concentrated formulation of rapid-acting insulin called lispro U-200, which may be more suitable for some patients because the volume of

insulin being injected is significantly less than U-100 insulins. It may also improve adherence for those who require large doses of insulin. However, concentrated insulins may be more expensive than U-100 insulins. Although U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk for dosing errors. In July 2016, the FDA approved a dedicated syringe for administering U-500 regular insulin from vials to help mitigate the risk for dosing errors.

Inhaled Insulin

Inhaled insulin is available for prandial use with a more limited dosing range. It is contraindicated in patients with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended for smokers or those who recently stopped smoking. It requires spirometry to identify potential lung disease in all patients before and after initiation of therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 U/kg per day) and the HbA_{1c} level remains above target, combination injectable therapy should be considered (Figure 2) (6). When this therapy is initiated, metformin therapy should be continued but other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens. Sulfonylureas, DPP-4 inhibitors, and GLP-1–receptor agonists may be continued or added to basal insulin therapy but are typically discontinued if a basal bolus or multiple-dose premixed insulin regimen is used. In patients with suboptimal blood glucose control, especially those requiring large doses of insulin, adjunctive use of a thiazolidinedione or SGLT-2 inhibitor may improve control and reduce the amount of insulin, although potential side effects should be considered. Once an insulin regimen is initiated, dose titration is important; dosing adjustments may be necessary in both mealtime and basal insulins, based on blood glucose level and an understanding of the pharmacodynamic profile of each formulation (that is, pattern control).

Further options for treatment intensification include adding a single injection of rapid-acting insulin analogue (lispro, aspart, or glulisine) before the largest meal, adding a GLP-1–receptor agonist, or stopping basal insulin and starting twice-daily premixed (or biphasic) insulin (such as 70/30 NPH/regular insulin mix, 70/30 aspart mix, or a 75/25 or 50/50 lispro mix). Administration is usually before breakfast and before dinner. A final option is once- or twice-daily 70/30 degludec/aspart mix taken before meals. Studies have shown the noninferiority of basal insulin plus a single injection of rapid-acting insulin administered at the largest meal compared with basal insulin plus a GLP-1–receptor agonist or 2 daily injections of premixed insulins (Figure 2). Basal insulin plus a GLP-1–receptor agonist is associated with weight loss and less hypoglycemia but may be more poorly tolerated and expensive than regimens using insulin alone (19, 20). The FDA recently approved 2 once-daily, fixed-ratio combination products containing basal insulin plus a GLP-1–receptor agonist—lixisenatide plus insulin glargine, and liraglutide plus insulin degludec. Both approaches have advantages and disadvantages. Providers can consider regimen flexibility when devising a plan for the initiation and adjustment of insulin therapy for patients with type 2 diabetes. For example, rapid-acting insulin offers greater flexibility in meal planning than premixed insulin. If one regimen does not achieve HbA_{1c} targets (for example, basal insulin plus a GLP-1–receptor agonist), another regimen should be considered (for example, basal insulin plus a single injection of rapid-acting insulin or twice-daily premixed insulin) (21, 22). Regular insulin and 70/30 NPH/regular insulin mix are less costly alternatives to rapid-acting and premixed insulin analogues, respectively, but their pharmacodynamic profiles may make them suboptimal.

Figure 2 also outlines recommendations for further intensification, if needed, to achieve glycemic goals. If patients who receive basal insulin plus a single injection of rapid-acting insulin before the largest meal still exceed their HbA_{1c} target, they should advance to a basal–bolus insulin regimen with 2 or more injections of rapid-acting insulin before meals. Providers should consider switching patients who receive twice-daily premixed insulin and still exceed their HbA_{1c} target to thrice-daily premixed insulin analogues (70/30 aspart mix or a 75/25 or 50/50 lispro mix). In general, these analogues have been found to be noninferior to basal–bolus insulin regimens with similar rates of hypoglycemia (23). If the HbA_{1c} targets are not being met or there are other patient considerations, providers should consider switching regimens (that is, from thrice-daily premixed insulin analogue to a basal–bolus insulin regimen or vice versa) (21, 22).

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Acknowledgment: The authors thank Matt Petersen; Erika Gebel Berg, PhD; and Sarah Bradley for their assistance in the review and editing of this manuscript. The 2017 Standards of Medical Care in Diabetes was developed by the ADA Professional Practice Committee: William H. Herman, MD, MPH (*Co-Chair*); Rita Rastogi Kalyani, MD, MHS (*Co-Chair*); Andrea L. Cherrington, MD, MPH; Donald R. Coustan, MD; Ian de Boer, MD, MS; R. James Dudl, MD; Hope Feldman, CRNP, FNP-BC; Hermes Florez, MD, PhD, MPH; Suneil K. Koliwad, MD, PhD; Melinda Maryniuk, MEd, RD, CDE; Joshua J. Neumiller, PharmD; and Joseph I. Wolfsdorf, MB, BCh.

Disclosures: Dr. Chamberlain reports personal fees from Merck, Janssen Pharmaceuticals, and Sanofi outside the submitted work. Dr. Herman reports work on data monitoring committees for Lexicon Pharmaceuticals and Merck Sharp & Dohme outside the submitted work. Dr. Rhinehart reports

personal fees from Sanofi, Janssen Pharmaceuticals, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Forest Pharmaceuticals, and AstraZeneca and other (employment and stock) from Glytec outside the submitted work. Dr. Skolnik reports personal fees and nonfinancial support from AstraZeneca and Sanofi and personal fees from Boehringer Ingelheim, Eli Lilly, and Teva outside the submitted work. Dr. Shubrook reports other from Lilly Diabetes (clinical trial and advisory board), AstraZeneca (clinical trial), Novo Nordisk (advisory board), and Takeda (clinical trial) outside the submitted work. Dr. Skolnik serves on the Primary Care Advisory Committee of the ADA. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-2937.

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