Review

Insulin Therapy for Type 2 Diabetes Mellitus

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IMPORTANCE The incidence and prevalence of type 2 diabetes mellitus are increasing.

OBJECTIVE To review currently available insulin therapy, as well as evidence on the use, application, initiation, and intensification of insulin in the outpatient setting.

EVIDENCE REVIEW Data sources included PubMed for trials and investigations in type 2 diabetes examining insulin use from January 1998 to April 2014.

FINDINGS The hemoglobin A_{1c} target for most patients with type 2 diabetes is 7% but needs to be modified when there is increased risk of hypoglycemia, reduced life expectancy, extensive comorbidities, or reduced resources. Insulin therapy may be considered early or late in the disease course; adverse effects include weight gain and hypoglycemia. Basal insulin can be added to oral hypoglycemic agents (generally stopping sulfonylureas) initially, and later, prandial insulin can be added in a stepwise fashion. Insulin treatment must be individualized, and there are a number of challenges to insulin initiation and intensification.

CONCLUSIONS AND RELEVANCE Insulin can help achieve ideal hemoglobin A_{1c} goals for patients with type 2 diabetes. Barriers such as adherence, patient preferences, clinician preferences, and resource allocation must be addressed.

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Diabetes mellitus affects more than 26 million people in the United States, with 90% to 95% having type 2 diabetes.[1] Two abnormalities result in type 2 diabetes: (1) insulin resistance, which causes an impaired ability of insulin to suppress hepatic glucose production and stimulate peripheral glucose uptake and (2) progressive impairment of insulin secretion.[2] Oral hypoglycemic agents (OHAs) reduce insulin resistance or facilitate insulin secretion and can be effective early in the course of disease.[2] Insulin is effective in all stages and often is ultimately necessary to achieve glycemic control.[3] Individual OHAs typically do not reduce hemoglobin A_{1c} (HbA_{1c}) levels by more than 1%.[4] Insulin has greater efficacy. Currently, 12% of patients with type 2 diabetes use insulin alone and 14% use insulin with OHAs.[1] Herein, we describe the types of insulin available, initiation of insulin in patients with type 2 diabetes, goals of insulin therapy, and opportunities for successful insulin use.

Methods

PubMed (January 2008–April 2014) was searched for articles that focused on *insulin* AND *type 2 diabetes* AND *glycemic control*, with further restriction to either controlled clinical trials, meta-analyses, or systematic reviews of insulin types, strategies for insulin therapy, or glycemic control methods with insulin. Additional PubMed searches (January 1998–April 2014) were completed for *barriers* AND *diabetes mellitus* AND *insulin* as well as *adherence* AND *diabetes mellitus* AND *insulin*.

To convert glucose from milligrams per deciliter to millimoles per liter, multiply by 0.0555.

Results

From the references of the 1596 studies identified, 169 additional studies were identified. Risks of intensive control with insulin were evaluated by examining outcomes from 7 large randomized clinical trials (type 2 diabetes, >1000 patients, >1000 person-years, minimum 3-year median follow-up, portion of blind assessment, prespecified outcomes, and insulin use in one or both treatment groups). Of 1765 articles reviewed overall, 100 met criteria and were included in this review. These studies included randomized trials, longitudinal observational studies, systematic analyses, reviews, and guidelines (**Figure 1** and **Figure 2**).

Goals of Therapy

Compared with HbA_{1c} levels greater than 7%, an HbA_{1c} level of 7% has been shown in randomized clinical trials to reduce the development and progression of the long-term microvascular complications of diabetes and is a reasonable goal of therapy.[5-7] Recent studies in type 2 diabetes have shown no benefit of inten-

sive therapy with an HbA_{1c} target of less than 7% for macrovascular complications during median follow-up periods ranging from 3 to 5 years.[8-10] In one study, an HbA_{1c} target of less than 6.0% was associated with possible harm compared with a target of 7.0% to 7.9%.[8]

Glycemic targets should be reconsidered for patients known to have increased risks of hypoglycemia, such as those with renal/liver failure or alcohol abuse.[3] Glycemic targets must also be individualized based on life expectancy, comorbidities, cardiovascular disease, diabetes duration, and resources.[3,11-14] Although guidelines do not specify HbA_{1c} targets for such patients,[11-14] Ismail-Beigi et al[15] proposed a target of approximately 8% for patients with these comorbidities or conditions, based on the fact that an HbA_{1c} target of 7.0% to 7.9% was associated with lower mortality and less hypoglycemia than a target of less than 6.0% in the ACCORD study.[16] The DCCT/EDIC study has shown that an increase in HbA_{1c} from 7% to 8% results in an absolute increase from 1 event per year to only 2 events per year of retinopathy progression.[17] Lower HbA_{1c} goals are appropriate for patients who are younger, for those who have not developed hypoglycemia, and when the benefits of microvascular disease protection outweigh the risks of hypoglycemia.

DPP-4 *dipeptidyl peptidase 4*
FPG *fasting plasma glucose*
GLP-1 *glucagon-like peptide 1*
HbA_{1c} *hemoglobin A_{1c}*
NPH *neutral protamine Hagedorn*
OHA *oral hypoglycemic agent*
SGLT-2 *sodium glucose transporter 2*

Box. Key Take-Home Messages

1. To prevent long-term complications, hemoglobin A_{1c} level should be maintained at 7% or less, but hemoglobin A_{1c} goals should be individualized according to patient age, comorbidities, available resources, and risks of hypoglycemia.
2. Insulin is often needed to achieve and maintain glycemic control as islet cell failure progresses over time in many patients with type 2 diabetes, and the appropriate insulin should be selected based on the pathophysiology of type 2 diabetes.
3. Insulin can be initiated with basal insulin and subsequently prandial insulin can be added using one of multiple strategies in a stepwise fashion. Therapy should be prescribed with attention to avoidance of hypoglycemia and mitigation of weight gain through lifestyle modification.
4. Clinicians must examine patient and health system barriers to insulin initiation and timely intensification.

When to Initiate Insulin Therapy

Insulin therapy is clearly indicated for patients in whom glycemic targets were not reached with 2 or more OHAs and for those who have severe hyperglycemia as indicated by fasting plasma glucose (FPG) levels higher than 250 mg/dL, HbA_{1c} levels higher than 10%, and/or symptoms of hyperglycemia.[3,11-14] Insulin can be given alone or in combination with OHAs.[3,11-14]

As HbA_{1c} targets are approached, postprandial glucose levels contribute more to overall glycemic control than FPG levels.[18,19] Adding mealtime rapid-acting analogs or OHAs to reduce postprandial glucose levels results in lower HbA_{1c} levels with less weight gain and less hypoglycemia compared with increasing basal insulin doses.[20]

Types of Insulin

The information in this section applies to both type 1 and type 2 diabetes except where specifically indicated. Modifications to the insulin molecule have resulted in analogs that either prolong its action (used as a basal insulin, which mimics the normal secretion of insulin overnight and between meals) or shorten its action (used preprandially to mimic insulin response to a meal). Regular and neutral protamine Hagedorn (NPH or isophane) insulins have durations of action intermediate between basal and rapid-acting analogs. The durations of action shown in **Table 1** are averages. The peak and duration of insulin action vary considerably among individuals. At higher doses, the durations of action are prolonged.[21,22]

Rapid-Acting Insulin Analogs

When administered 0 to 15 minutes before meals, rapid-acting analogs resemble physiologic insulin increases stimulated by food.[22] In patients with gastroparesis or poor appetites, insulin can be injected halfway through or after the meal; doses can also be adjusted proportionate to food consumed.[22]

Short-Acting Insulin

Regular insulin should be given about 30 minutes before meals. Meta-analyses show that rapid-acting analog insulin provides better control of postprandial glucose levels, less hypoglycemia, and increased flexibility in administration timing compared with regular insulin.[23-25]

Intermediate- and Long-Acting Insulin Analogs

Neutral protamine Hagedorn insulin generally requires twice-daily dosing.[22] There is considerable interindividual and intra-individual variability in the timing of peak and maximal levels, making the glucose responses relatively unpredictable.[21,26,27]

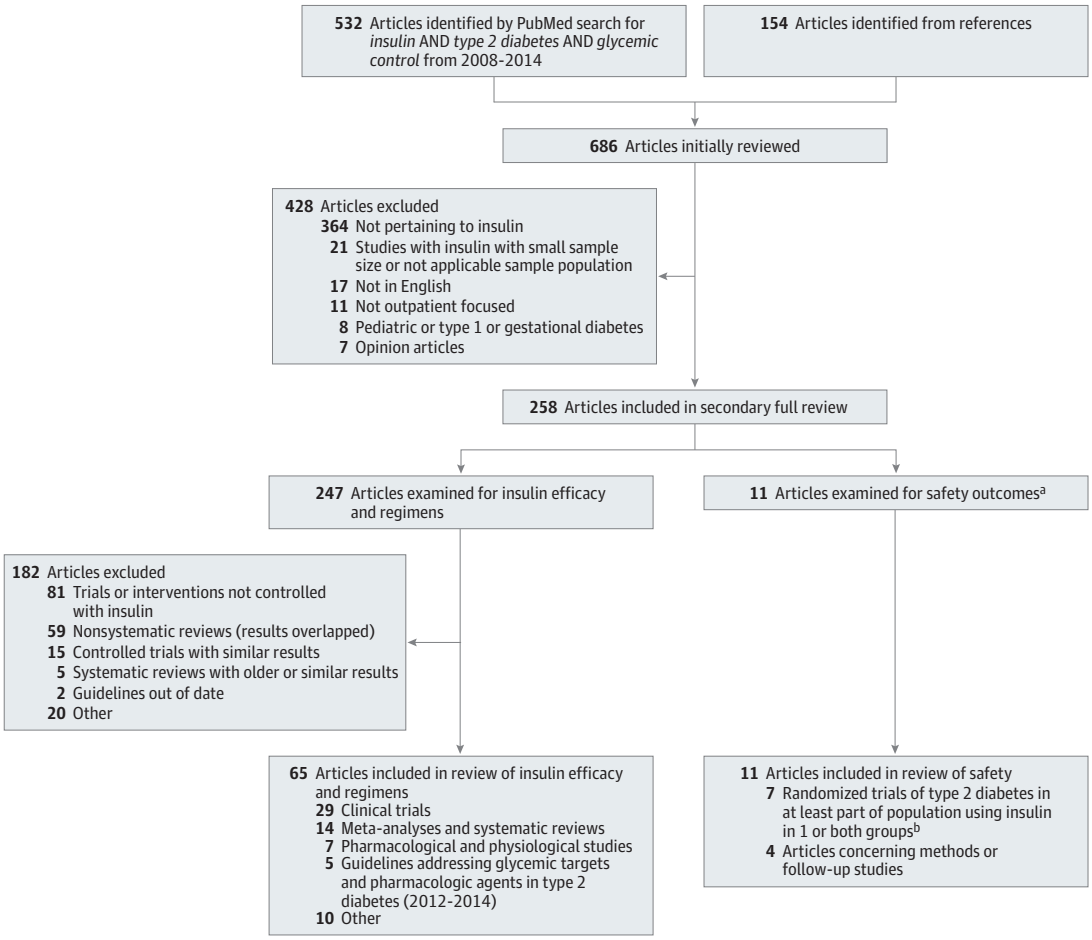
Glargine insulin typically requires once-daily dosing. Occasionally, patients receiving high doses may require twice-daily dosing of glargine, while insulin detemir often necessitates twice-daily dosing.[22] A meta-analysis showed that 13.6% to 57.2% of patients inject insulin detemir twice daily.[28] Both have considerably less day-to-day variability of action duration compared with NPH insulin.[27] Available evidence from randomized trials in type 2 diabetes[23,24,29-34] show that once-daily glargine or insulin detemir provide similar HbA_{1c} lowering but less hypoglycemia compared with twice-daily NPH insulin. Insulin detemir is more expensive than NPH insulin but is associated with higher quality-adjusted life-years because of the decreased incidence of hypoglycemia and incremental cost-effectiveness ratios.[35,36] However, if cost is a major concern, NPH insulin is a reasonable therapy, since the absolute difference in hypoglycemia rates is small.

Premixed Insulins

Premixed insulins are usually given before breakfast and dinner (Table 1). Because 2 different insulin types are present, dosing needs to reflect the peaks of both insulin forms. Twice-daily dosing is the main advantage of premixed insulins. Their use restricts adjustment of doses and restricts timing of meals because both types of insulin have to be adjusted simultaneously.

Short-term studies suggested that premixed regimens had similar or better glycemic control but increased hypoglycemia compared

Figure 1. Initial Publication Search, 2008-2014



[a] Trials were examined for safety outcomes if they were large randomized clinical trials in diabetes mellitus and had adult patient populations, blind assessment, and prespecified outcomes and reported results from January 1998 to April 2014.

[b] The appendixes of all 7 randomized trials were reviewed.

with basal insulin alone.[37-40] A large 3-year type 2 diabetes study demonstrated that premixed insulins provided inferior glycemic control and more hypoglycemia than basal insulin alone.[40] Basal-bolus insulin leads to better glycemic control compared with premixed insulin.[39]

U-500 Insulin

Most insulin has 100 U/mL. "U-500" regular insulin (500 U/mL), because of its high concentration, has a substantially prolonged and variable duration of action. It is typically administered 2 to 3 times daily without basal insulin.[41,42] U-500 insulin is used in patients with severe insulin resistance (>200 U/d).[42] Confusion may occur when administering U-500 insulin with U-100 syringes, especially if clinicians, pharmacists, nurses, and patients are unfamiliar with its use.

Indications, Methods, and Strategies for Insulin Administration When Oral Therapy Alone Fails

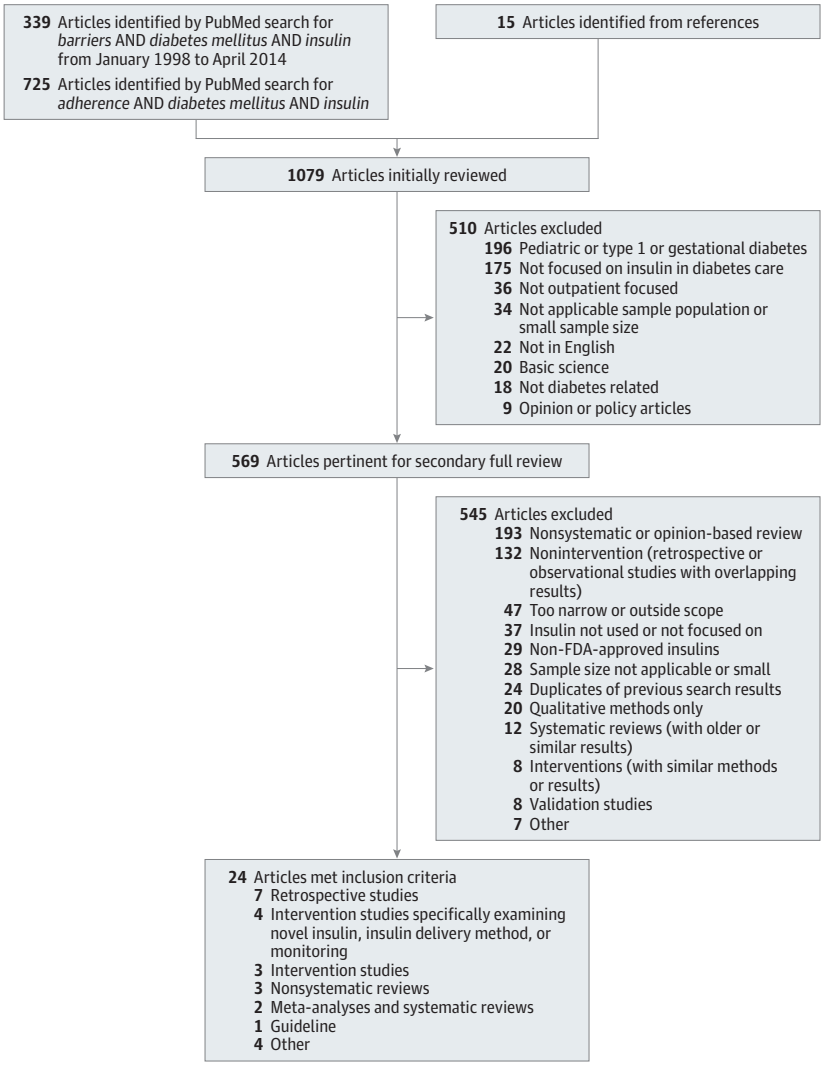
Addition of Long-Acting Basal Insulin to an Oral Regimen

Similar FPG and HbA_{1c} levels with less hypoglycemia and better evening glucose levels are achieved when glargine or insulin detemir, vs NPH or twice-daily premixed insulin, is added to OHA regimens.[23,24,29-34,40,43,44] Hemoglobin A_{1c} levels of less than 7% can be achieved in approximately two-thirds of patients with either glargine[29] or insulin detemir[30] alone without prandial insulin when added to metformin. Therefore, glargine or insulin detemir rather than NPH insulin is recommended as the next step when glucose goals are not reached with OHAs or when a glucagon-like peptide 1 (GLP-1) receptor agonist is not being considered (**Figure 3**).[3] An initial dose of 10 U can be adjusted upward until the FPG target range is reached.

Intensification of Insulin Regimens

Prandial insulin is indicated in patients whose HbA_{1c} remains high despite attaining targeted fasting glucose levels using basal insulin. Prandial analog insulin can be added stepwise, initially to the largest meal of the day and then to second and third meals at 8- to 12-week intervals if HbA_{1c} targets are not met (Figure 3). An initial dose of 2 to 4 U can be increased by 1 to 2 U every 3 days if the glucose level before the next meal is not at the goal of 70 to 130 mg/dL. Using this stepwise approach, Meneghini et al[45] found that after 48 weeks,

Figure 2. Subsequent Publication Searches, 1998-2014



FDA indicates US Food and Drug Administration.

HbA_{1c} decreased by 1.2% and 75% of patients were using 3 injections of prandial insulin per day. Even a single injection of rapid-acting insulin prior to the main meal improves glucose control.[46] Davidson et al[47] found that after 24 weeks, reductions in HbA_{1c} were 0.44%, 0.36%, and 0.43% with 1, 2, or 3 injections of glulisine, respectively, when added to glargine. When a patient does not wish to use more than 2 injections per day, the preferred approach is a daily long-acting basal insulin and a prandial rapid-acting insulin with the largest meal rather than premixed insulins.

Prandial insulin can be adjusted for meal size using carbohydrate counting, in which the insulin dose is based on the quantity of the meal's carbohydrates.[48-50] This method can be complex. If meals are consistent, a simple algorithm for adjusting doses based on premeal blood glucose levels is as effective as carbohydrate counting.[48] Alternatively, fixed-dose prandial insulin prescriptions can be helpful, have similar efficacy to carbohydrate-counting dosing, are simpler, and lead to greater treatment adherence.

Insulin doses can be titrated (Figure 3) independently by able and willing patients, with guidance as needed from their clinicians until goal ranges are reached. Patient-managed titration algorithms for basal and prandial insulins are as effective as physician-managed algorithms.[51] Clinician and patient resources must be used appropriately to implement titration schedules safely and effectively. Reviewing management in different real-life scenarios (modeled decision making), stepwise insulin initiation, and limited reliance on carbohydrate counting can assist in developing an individualized outpatient titration schedule, as was demonstrated in ACCORD.[16] Initiation and intensification of therapy can be opportunities for review of glycemic goals and actions of insulin and to encourage patient empowerment.

Role of OHAs Following Insulin Initiation or Intensification

In a patient with type 2 diabetes, the first step of therapy is lifestyle change and metformin therapy unless HbA_{1c} is greater than 9%, in which case insulin therapy can be considered. If the HbA_{1c} target is not met, a second OHA or a GLP-1 receptor agonist can be added. If the HbA_{1c} target is still not reached, a third OHA, a GLP-1 receptor agonist (if not added previously and therapy does not include a di-

Table 1. Pharmacokinetic Properties of Therapeutic Insulins

Insulin	Time of Action			Cost, $[a]	Comments
	Onset	Peak	Duration		
Long-acting					Peakless, reproducible; cannot mix with other insulins
Glargine	2-4 h	None	20-24 h	207	
Detemir	1-3 h	6-8 h	18-20 h	207	
Intermediate-acting					Variable action profile; can mix with rapid-acting insulins Possible role in steroid hyperglycemia
NPH	2-4 h	4-10 h	10-18 h	92	
Short-acting					Longer duration profile is useful in gastroparesis
Regular	~30 min	2-4 h	5-8 h	92	
Rapid-acting					Can be given postprandially in gastroparesis; postprandial dose adjustments for incomplete meals
Aspart	5-15 min	0.5-2 h	3-5 h	183	
Lispro	5-15 min	0.5-2 h	3-5 h	182	
Glulisine	5-15 min	0.5-2 h	3-5 h	170	
Premixed					Simple to administer; cannot adjust each component separately
70% NPH/30% regular	0.5-1 h	3-12 h (dual)	10-16 h	92	
75% NPL/25% lispro	5-15 min	1-4 h (dual)	10-16 h	189	
50% NPL/50% lispro	5-15 min	1-4 h (dual)	10-16 h	189	
70% NPA/30% aspart	5-15 min	1-4 h (dual)	10-16 h	189	
U-500 insulin	~30 min	4-8 h	14-15 h	96[b]	Use in patients with severe insulin resistance who need large doses; give 2 or 3 times daily without basal insulin

Abbreviations: NPA, neutral protamine aspart; NPH, neutral protamine Hagedorn; NPL, neutral protamine lispro.

[a] Per 10-mL (1000-U) vial. Costs obtained from http://www.goodrx.com on April 25, 2014.

[b] Per 2 mL (1000 U). Cost obtained from http://www.goodrx.com on April 25, 2014.

peptidyl peptidase 4 [DPP-4] inhibitor), or insulin can be added.[3,12-15] Continuing a sulfonylurea after initiating insulin allows for better management of postprandial increases in glucose,[52] but sulfonylureas are often ineffective by the time a patient needs insulin, and they increase hypoglycemia risk.[53] In a pooled analysis of 11 clinical trials, HbA_{1c} lowering and hypoglycemic risks were better when glargine was added to metformin alone compared with when glargine was added to a sulfonylurea alone or a sulfonylurea-metformin combination.[54] Glucagon-like peptide 1 receptor agonists increase insulin, lower glucagon secretion, delay gastric emptying, and cause weight loss. Dipeptidyl peptidase 4 inhibitors block the degradation of GLP-1, increasing endogenous GLP-1 levels.[55] The combination of DPP-4 inhibitors or injectable GLP-1 receptor agonists with insulin may improve periprandial control, limit insulin requirements, and lower risks of hypoglycemia and weight gain.[55-58] Pioglitazone with insulin causes more edema than either drug alone.[59] It is recommended that only metformin, sodium glucose transporter 2 inhibitors, and DPP-4 inhibitors or GLP-1 agonists be continued when insulin is added.[3]

Insulin Treatment of Patients With Severe Hyperglycemia

Patients occasionally present with FPG levels greater than 250 mg/dL (HbA_{1c} >10%) and have substantial glucose toxicity, a phenomenon in which high glucose levels inhibit insulin secretion as well as insulin action.[60] Glucose toxicity can be reversed with insulin therapy.[60] A starting basal/bolus insulin regimen has been recommended with a total dose of 0.5 U/kg, half basal and half prandial, divided into 3 preprandial portions.[61] Total doses greater than 0.6 U/kg cause significantly more hypoglycemia than doses of 0.2 U/kg or less.[62] Lower starting total daily doses (eg, 0.25 U/kg) should be considered in patients with estimated glomerular filtration rate levels of less than 45 mL/min/1.73 m^2,[63] those with a body mass index of less than 20, and those older than 65 years.

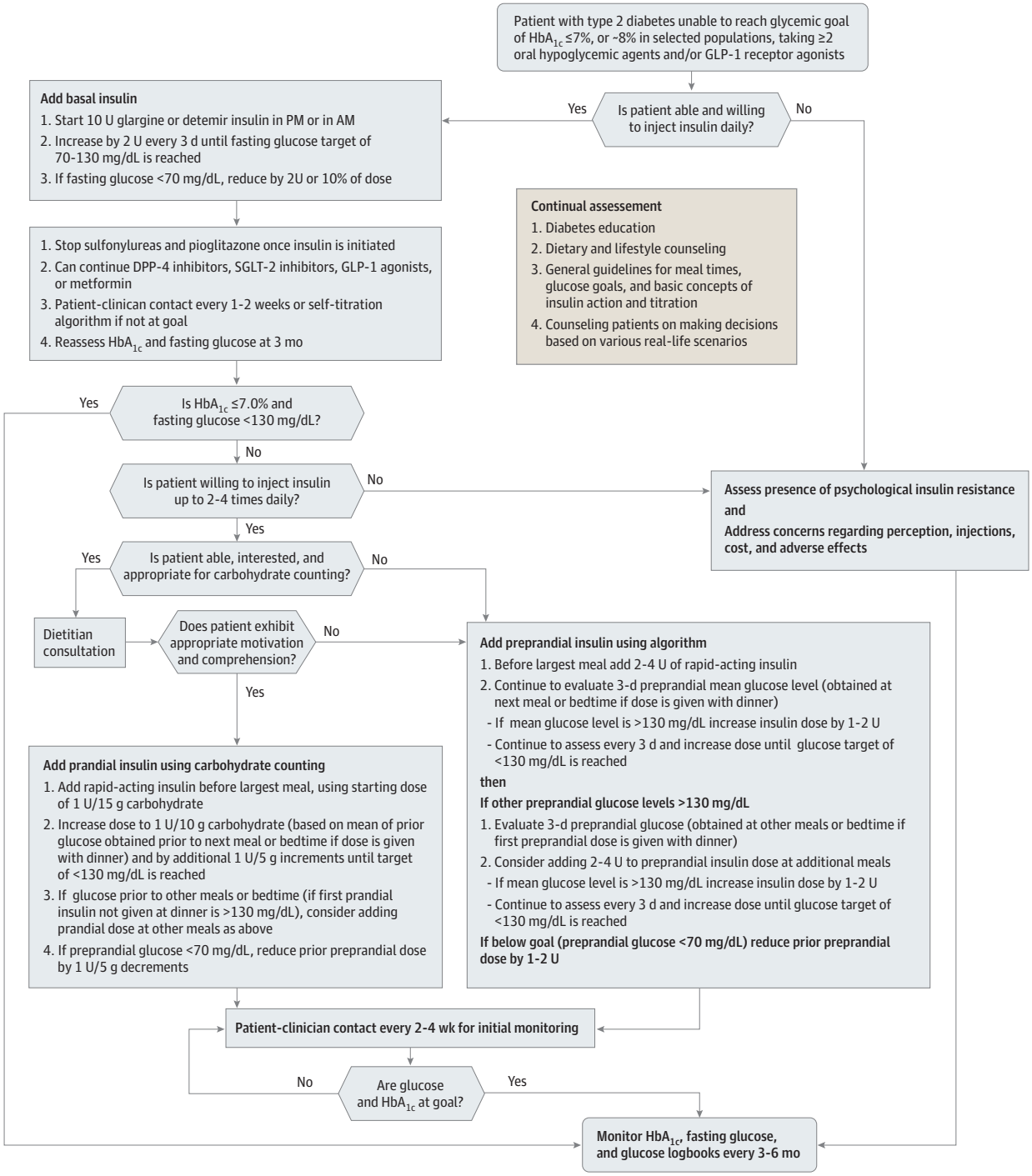
As glucose toxicity improves, insulin doses may be reduced substantially. Alternatively, many patients may be able to maintain glycemic control when switching to OHA or GLP-1 receptor agonist treatment alone, especially patients whose glucose is well controlled with less than 0.42 U/kg of insulin.[64-66]

Observational studies and prospective randomized trials show that intensive insulin therapy can improve β-cell function early in the course of diabetes through reversal of glucotoxicity and lipotoxicity.[67-71] A meta-analysis showed that a short course of insulin (14-21 days) in patients with newly diagnosed type 2 diabetes (baseline HbA_{1c} of 9.7%-11.9% and body mass index of 24-27.7) had beneficial effects on homeostatic model assessment of β-cell function and insulin resistance, with up to 46% of treated patients achieving a 12-month drug-free remission.[72] One study demonstrated preservation of the acute insulin response to a glucose stimulus,[70] indicating a possible role for short-term use to potentially modify disease course.

Risks of Insulin Therapy

In the UK Prospective Diabetes Study (UKPDS), insulin therapy resulted in more weight gain and hypoglycemia compared with conventional treatment[6,7] (eTable in the Supplement). There were no significant effects on cardiovascular events or death related to any treatment in the original study.[6,7] However, at 10-year follow-up, there were benefits of intensive therapy on cardiovascular out-

Figure 3. Suggested Algorithm for Initiating Insulin in Patients With Type 2 Diabetes



This suggested approach has not been validated in randomized trials. HbA_{1c} indicates hemoglobin A_{1c}; GLP-1, glucagon-like peptide 1; SGLT-2, sodium glucose cotransporter 2; and DPP-4, dipeptidyl peptidase 4.

comes (15% relative reduction in myocardial infarction [*P*=.01] and 13% relative reduction in all-cause mortality [*P*=.007]), along with a reduction in all diabetes-related outcomes (absolute risk, 48.1 vs 52.2 events per 1000 patient-years; relative risk, 0.91; 95% CI, 0.83-0.99).[73] Recent trials have shown significant weight gain (1-3 kg over 24 weeks) and hypoglycemia with insulin use.[8-10,29,30] The long-term effects of episodic mild or severe hypoglycemia remain unknown. Intensification of treatment targeting HbA_{1c} levels of less than 7% with multimodal therapy that included insulin showed no additional cardiovascular benefit in ADVANCE and VADT and pos-

sible harm in ACCORD.[8-10] The increased mortality in ACCORD was associated with the highest on-treatment HbA_{1c} levels, was not attributable to hypoglycemia, and has not been explained fully.[74,75] ORIGIN, a trial that evaluated the role of glargine in early-stage/moderate hyperglycemia (impaired FPG, impaired glucose tolerance, diabetes with 0 or 1 oral agent, and a glycated hemoglobin level <150% of the upper limit of normal), found no effect of insulin use on cardiovascular or cancer outcomes.[76] Glargine reduced the development of new-onset diabetes but caused weight gain and hypoglycemia.[76]

Barriers to Implementation, Psychological Insulin Resistance, and Adherence

Cost, adherence, patient preferences and the diversity of treatment methods affect outcomes. A small proportion of those with diabetes achieve appropriate glycemic and cardiovascular risk factor targets, making clear the need for proven methods that improve care in real life.[77,78] In a study of commercially insured patients in the United States, there were significant departures from guideline-recommended insulin therapies and a lack of insulin intensification.[79] Examination needs to occur of the reasons for delayed initiation and intensification of insulin and factors affecting "psychological insulin resistance" in both health care professionals and patients.[80,81] Up to one-third of patients report being unwilling to start insulin if recommended and express a myriad of negative beliefs about insulin, and in the United States, perceived efficacy is low, while self-blame is high.[82,83]

Adherence to insulin (60%-80%) is lower than adherence to OHAs and is lower in patients enrolled in Medicaid and in patients with frequent dosing schedules.[84] Factors affecting adherence include regimen comprehension, perception of benefits, adverse effects, regimen costs (insulin, syringes, glucose strips), regimen complexity, and emotional well-being.[84] A systematic review of barriers to insulin progression revealed that there were no prospective, methodologically rigorous, broadly focused research articles examining these issues.[85] Patient costs may guide decision making, even though economic and clinical benefits of insulin initiation and intensification have been shown.[86,87]

Patients with prior insulin experience had fewer concerns about injections and intensification compared with insulin-naive patients but had more concerns about adverse effects, maintenance of glycemic control, and hypoglycemia avoidance.[85] Clinician barriers include physician-nurse discrepancy on plan of care, clinician experience/adequate resources, perception of patient capabilities, and, less often, national guideline or reimbursement difficulties.[85] Interventions to address barriers to implementation include shared decision aids, computer-assisted management/problem-solving tools, and cognitive behavioral therapy for concomitant depression; all interventions had favorable results but nominal changes in hard glycemic end points (significant change in HbA_{1c} or proportion of patients within goal).[88-90]

New Insulins, Delivery Methods, and Monitoring Technologies

Two new ultra long-acting insulins, insulin degludec and LY2605541, are undergoing testing in phase 3 clinical trials and, compared with glargine, show similar efficacy but less hypoglycemia with daily injections in patients with type 2 diabetes.[91-93] Technosphere insulin, a new inhaled formulation, has been approved by the US Food and Drug Administration.

Insulin is available in prefilled pens in which the dose is dialed in and needles are changed between doses. These pens are being used increasingly because of their convenience, greater accuracy, and patient preference.[94] Their major limitation is higher patient cost and insurance coverage, although total annualized health costs may be lower and adherence improved.[95,96] Patients in 23 of 24 studies preferred pens to syringes, citing ease of use, acceptability, convenience, and perceived efficacy.[97]

Continuous insulin infusion (pump) therapy in patients with type 2 diabetes can be considered in those with severe insulin resistance and poor control.[98,99] Newer mechanical patch pumps are currently being tested in randomized trials.[99] Continuous glucose monitoring has been recommended in patients with type 2 diabetes to detect nocturnal hypoglycemia, increased insulin resistance in the morning (dawn phenomenon), postprandial hyperglycemia, and hypoglycemic unawareness and can be used during major regimen changes.[100]

Comparison With Clinical Practice Guidelines

Clinical recommendations are available from the American Diabetes Association (ADA)[12] (modeled on the position statement of the ADA/European Association for the Study of Diabetes),[3] the guidelines of the UK National Institute for Health and Care Excellence (NICE),[13,14] and the International Diabetes Federation (IDF)[15] (**Table 2**). All support using a multidisciplinary team, including diabetes educators, and lifestyle counseling. The ADA guideline states that glargine and insulin detemir are preferred to NPH insulin, rapid-acting insulins are preferred to regular insulin, and premixed insulins should be avoided. Neither the NICE[13,14] nor the IDF[15] guidelines recommend against premixed insulin use. The HbA_{1c} targets are similar at less than 7% for the ADA and NICE but less than 6.5% for the IDF. Because data from randomized studies demonstrate benefit at 7% and not below,[5-7] the recommendation herein is 7% or less rather than less than 7%. The preprandial target glucose range recommendations are, for the ADA, 70 to 130 mg/dL[12]; for NICE, less than 126 mg/dL[13,14]; and for the IDF, less than 116 mg/dL.[15] In patients prone to hypoglycemia, 80 mg/dL as a lower boundary could be considered. The initial dose of basal insulin of 10 U that we recommend is in the lower portion of the range recommended by the ADA (0.1-0.4 U/kg)[12] to avoid hypoglycemia and simplify dosing.

All 3 guidelines emphasize the need for patient-centeredness, highlighting age, attitudes, disease duration, comorbidities, and resources, which affect decision making in both therapy and glycemic targets.[12-15] Guidelines do not emphasize specific evidence-based recommendations on methods to systematically assess adherence or address barriers to initiation and intensification of insulin.

Discussion

In patients with type 2 diabetes, the first step of therapy is lifestyle change and metformin unless HbA_{1c} is greater than 9%, in which case insulin can be considered. If the HbA_{1c} target is not met, a second OHA or a GLP-1 receptor agonist can be added. If the HbA_{1c} target is still not reached, either a third OHA, a GLP-1 receptor agonist (if not

Table 2. Comparison of Approaches for Patients With Type 2 Diabetes Based on Current Review With Current Guidelines From the ADA/EASD, IDF, and NICE[a]

	Approach Based on Current Review	ADA/EASD Patient-Centered Approach[3,11]	IDF[14]	NICE[12,13]
Hemoglobin A_{1c} target	≤7% or ~8% in selected populations	<7%	<7.0%	6.5%
Glucose targets, mg/dL				
Preprandial	70-130[b]	70-130	<116	≤126
Postprandial	<180	<180	<160	<153
Multidisciplinary team management	Yes	Yes	Yes	Yes
Consider insulin initially	Hemoglobin A_{1c} ≥10% or consider if >9%	Consider if hemoglobin A_{1c} ≥9% Strongly consider if >10%		
Start basal insulin	After 2-3 oral agents and not at goal, start glargine or insulin detemir, 10 U/d	After 2-3 oral agents and not at goal, start glargine or insulin detemir, 0.1 -0.4 U/d	After 2-3 oral agents and not at goal, start NPH, glargine, insulin detemir, or premixed insulin	After 2 oral agents and not at goal start NPH, glargine, insulin detemir, or premixed insulin
Basal insulin titration	Increase by 1-2 U/d every 3 d until FPG goal of 70-130 mg/dL is reached or by 4 U/d every 3 d if FPG >180 mg/dL	Increase by 1-2 U/d 1-2times per wk until FPG goal of 70-130 mg/dL is reached	Increased by 2 U every 3 d until FPG goal of <115 mg/dL is reached	No titration schedule given
Add prandial insulin	If not at goal with basal insulin, add 2-4 U stepwise 1 meal at a time, starting at largest meal	If not at goal with basal insulin, add stepwise 1 meal at time, starting at largest meal	If not at goal with basal insulin	If not at goal with basal insulin
Prandial insulin titration	Increase dose by 1 U (if basal insulin dose ≤10 U) or by 2 U (if basal insulin dose >10 U) based on 3-d average of glucose levels before next meal until target 70-130 mg/dL reached Can add insulin at second and third meals if necessary and able	Not specifically outlined	Not specifically outlined	Not specifically outlined
Premixed insulins	Titration of both basal and prandial needed simultaneously	Titration of both basal and prandial needed simultaneously	Can be used	Can be used
Assessment	Assess resource limitations and patient capability for monitoring; initiation and intensification require frequent monitoring depending on resources and patient preference	Frequent monitoring, continual assessment, utilization of remote resources when able (telephone, e-mail)	Annual review assessment with protocol -driven care at routine visits Assess every 3 mo Provide telephone contact	2- to 6-mo intervals
Addressing barriers	Patient: assess comprehension, perceptions, adherence, cost, regimen complexity, depression Clinician: assess own perceptions, limitations, resources, health system barriers to care Both: assess psychological insulin resistance	Concentration on patient-centered approach Sequential insulin strategies with assessment of flexibility and patient comprehension ADA practice recommendations: align with chronic care model	Concentration on structured guidelines, protocols, audits of glucose control of patients taking oral medications Collaboration, sensitivity to culture, mutual care plan highlighted	Concentration on patient-centered care Structured programming and education, self-care, and good communication highlighted

Abbreviations: ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; IDF, International Diabetes Federation; NICE, National Institute for Health and Care Excellence.

[a] The sections on insulin apply specifically to type 2 diabetes but the other sections apply to both types.

[b] Consideration should be given to an increased lower boundary; eg, 80 mg/dL in patients prone to hypoglycemia.

added previously and no treatment with a DPP-4 inhibitor), or insulin can be added.[3,12-15]

The goal of glycemic control is an HbA_{1c} of 7.0% or less unless hypoglycemia ensues, to prevent or delay the long-term complications of diabetes.[12-14] Glycemic targets should be higher in patients at increased risk of hypoglycemia and those with decreased life expectancy, cardiovascular disease, comorbidities, diminished resources, or insurmountable psychological barriers.

Although a single injection of long-acting insulin added to OHAs often achieves glucose control for several years, many patients require intensification of insulin therapy later, with the addition of rapid-acting insulin before 1 or more meals. A number of patient and clinician barriers often need to be overcome, such as patient costs, despite proven overall cost-effectiveness of treatment.[8,6]

Several research questions remain unanswered. What are the long-term risks of insulin-related weight gain and hypoglycemia? How can advancements in insulin preparations, administration, and monitoring techniques improve outcomes, and which patients benefit most from new therapies with regard to cost-effectiveness and safety? What are the barriers to adherence to insulin, OHAs, and GLP-1 receptor agonists from a comprehensive

perspective (health system and society)? Can late readdition of nonsecretagogue oral agents combat the adverse effects of intensive insulin regimens?

Recognizing and overcoming psychological insulin resistance in both patients and clinicians are necessary to help achieve optimal outcomes. Clinical trials data guide therapy and are used to formulate guidelines; however, insight is needed on implementation methods to improve care. Practitioners should examine their strengths, knowledge base, and resource availability and identify opportunities to improve care. All clinicians may benefit from understanding more about the methods of decision making to help patients make appropriate, effective choices about their diabetes care and insulin therapy.

Conclusions

Insulin can help achieve ideal hemoglobin A_{1c} goals for patients with type 2 diabetes. Barriers such as adherence, patient preferences, clinician preferences, and resource allocation must be addressed.

ARTICLE INFORMATION

Author Contributions: Drs Wallia and Molitch had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Wallia, Molitch.
Acquisition, analysis, or interpretation of data: Wallia, Molitch.
Drafting of the manuscript: Wallia, Molitch.
Critical revision of the manuscript for important intellectual content: Wallia, Molitch.
Administrative, technical, or material support: Molitch.
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