Commentary

Primary Care Management of Patients With Type 2 Diabetes: Overcoming Inertia and Advancing Therapy With the Use of Injectables

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ABSTRACT

Type 2 diabetes (T2D) is a progressive disease caused by insulin resistance and associated progressive β-cell functional decline, as well as multiple other related metabolic and pathophysiologic changes. Left unchecked, T2D increases the risk of long-term microvascular and cardiovascular complications and is associated with excess morbidity and mortality. Despite multiple effective options for reducing hyperglycemia, patients are not optimally managed, largely due to delays in appropriate and timely advancement of therapy. Glucagon-like peptide-1 receptor agonists and basal insulin are recommended by treatment guidelines as effective options for advancing therapy to achieve glycemic control. However, injected therapies often face resistance from patients and clinicians. Glucagon-like peptide-1 receptor agonists are associated with weight loss, low risk of hypoglycemia, and potential beneficial cardiovascular effects. The class is recommended for patients across the spectrum of disease severity and represents an attractive option to add to basal insulin therapy when additional control is needed. Newer second-generation basal insulin analogues offer advantages over first-generation basal insulins in terms of lower hypoglycemia rates and greater flexibility in dosing. Incorporating injectable therapy into patient care in a timely manner has the potential to improve outcomes and must not be overlooked. Primary care clinicians play a significant role in managing patients with T2D, and they must be able to address and overcome patient resistance and their own barriers to advancing therapy if optimal treatment outcomes are to be achieved. The purpose of this expert opinion article was to provide a commentary on the key principle of advancing therapy with injectables to control hyperglycemia. (*Clin Ther*. 2019;41:352–367)

keywords: Type 2 diabetes, Hyperglycemia, Clinical inertia, Patient education, Primary care.

INTRODUCTION

Type 2 diabetes (T2D) is principally a disease of insulin resistance and progressive β-cell failure, but multiple pathophysiologic processes (the so-called "ominous octet") contribute to its development and progression (as summarized by DeFronzo[1]). Hyperglycemia develops and progresses as β cells fail, and insulin secretion becomes inadequate to compensate for or overcome insulin resistance. In this process, postprandial hyperglycemia in response to meals or administered glucose occurs early, followed by fasting hyperglycemia.[2] It has been estimated that patients' β-cell function may already be diminished by up to 50% at the time of diagnosis,[3] whereas hallmarks of the metabolic syndrome, represented by insulin resistance, dyslipidemia, hypertension, and its attendant risks of cardiovascular (CV) events, may be

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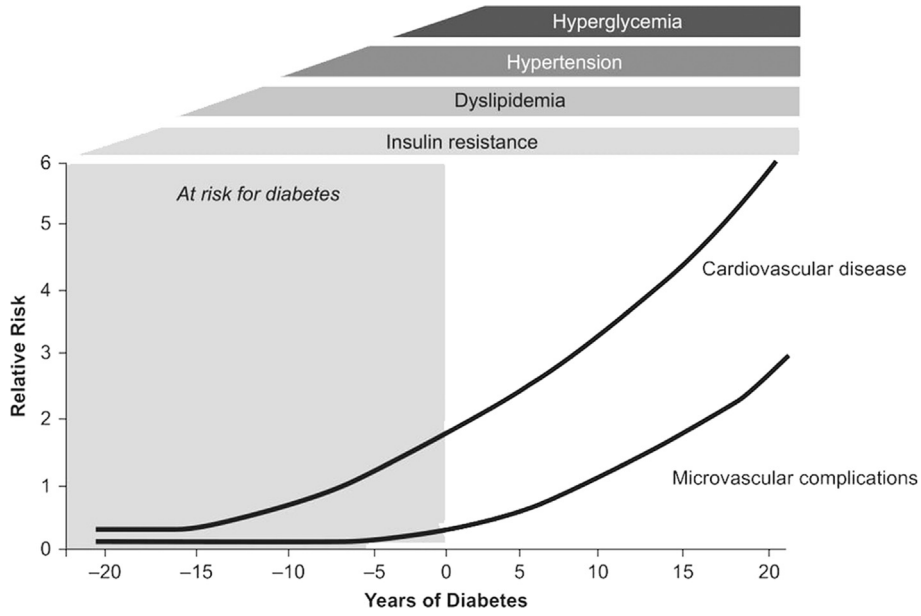


Fig. 1. Life cycle and risk of complications of type 2 diabetes. Reproduced from Kendall and Bergenstal[4] with permission from Intellisphere, LLC ©2018.

present for as long as 10 years before diagnosis (Fig. 1).[4] Although patients may retain residual insulin response, the progressive nature of T2D means that many patients eventually will require injectable therapies, which currently include insulin therapy and the class of glucagon-like peptide-1 (GLP-1) receptor agonists (RAs).[5–7]

In patients with T2D, maintaining near-normal blood glucose levels mitigates the risk of complications,[8,9] yet one half of patients are not achieving glycemic goals.[10] Despite pharmacologic advancements, there has been a recent decline in the proportion of patients with T2D who maintain glycosylated hemoglobin (A_{1c}) levels <7.0% and a concomitant increase in those with A_{1c} levels >9.0%. Poor glycemic control is likely to be multifactorial (Fig. 2).[5,6,10] A_{1c} goals not being achieved often results from delays in advancing therapy as needed for patients inadequately controlled on their current diabetes medications,[11–13] with one study showing a median time to insulin initiation of >7 years despite A_{1c} levels >8.7%.[10] Multiple clinician and patient barriers contribute to this clinical inertia, with glycemic targets not being reached, and poor outcomes as the consequence; part of this problem may be that clinicians are not managing patients optimally or as recommended in national guidelines.[14–17]

The present article provides a commentary on the key principle of advancing therapy with injectables to control hyperglycemia. Information for this commentary was obtained from references identified by using MEDLINE searches, the bibliographies of articles identified during the searches, regulatory documents, and published guidelines, and selected by the authors to reflect their experience and opinions.

CURRENT MANAGEMENT OF T2D

Early intervention to achieve good glycemic control has lasting benefits in preserving β-cell function, duration of response, and reduced rates of complications, as reported in long-term follow-up of patients.[8,18–20] Patients with T2D in a large US health care system who achieved A_{1c} levels <7.0% within 1 year of initiating treatment had substantially longer times to treatment failure than those whose A_{1c} levels remained in the range of 7.0%–7.9%.[20] Landmark clinical trials in T2D showed a reduction in some microvascular complications, including nephropathy, peripheral neuropathy, and retinopathy, and a trend toward reduced risks of heart attack and all-cause

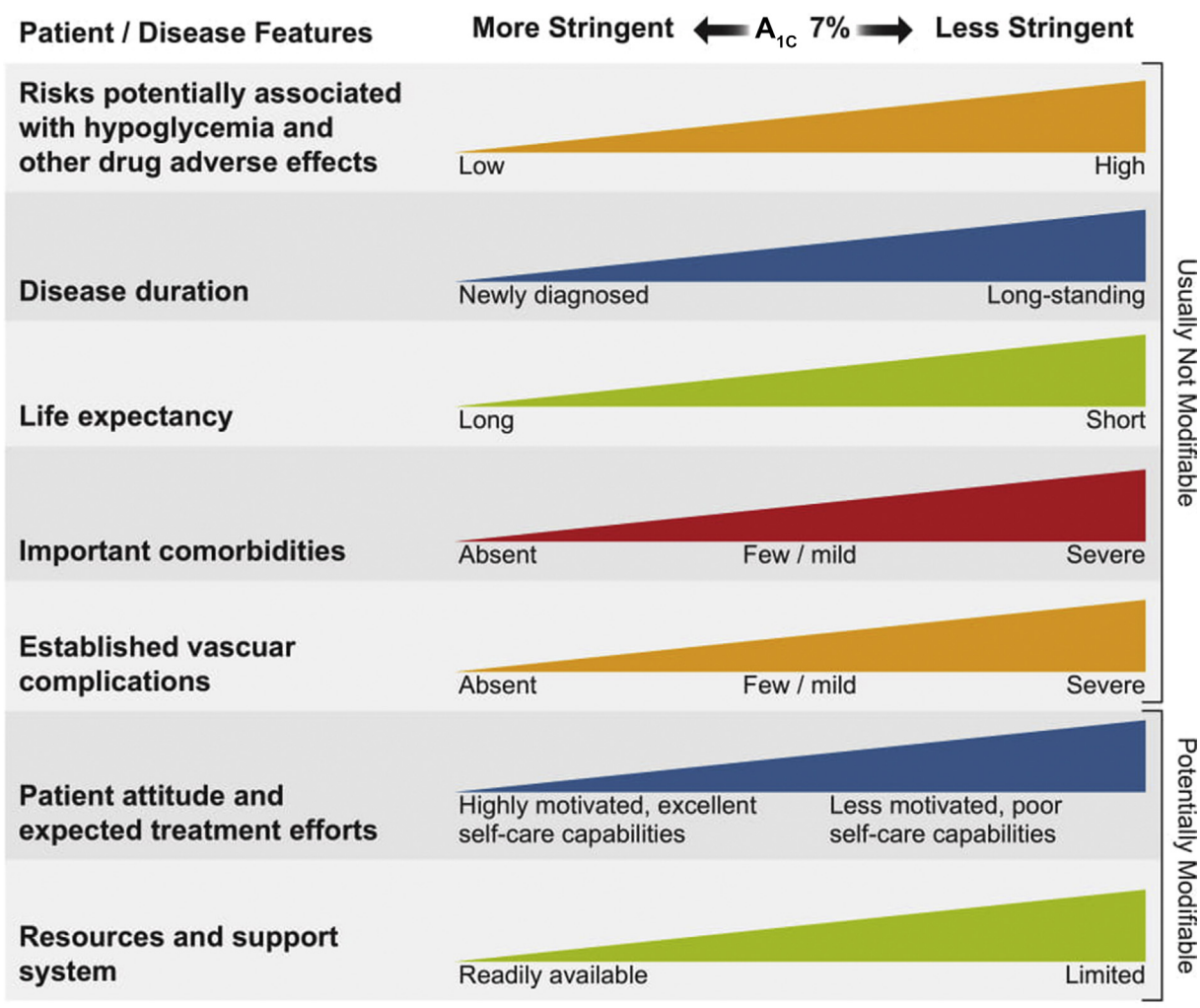
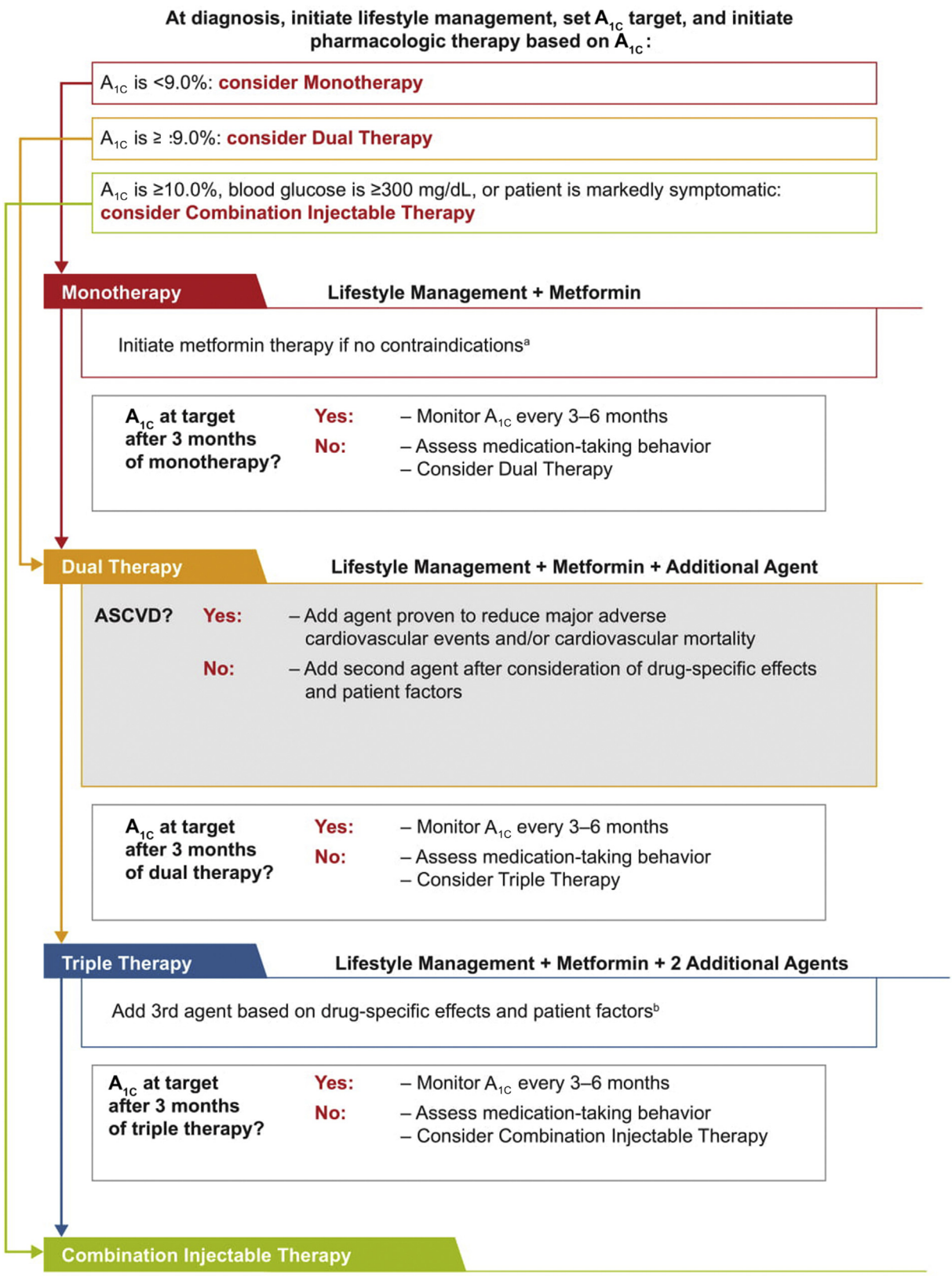


Fig. 2. Patient and disease factors to consider in setting glycemic goals for patients with type 2 diabetes. A_{1c} = glycosylated hemoglobin. Reproduced from ADA 2018[32] with permission from ADA ©2018.

mortality in patients treated with intensive glucose-lowering therapy.[9,21–23] Data on beneficial effects on peripheral neuropathy were mixed in early trials,[21–23] although, overall, more recent trials suggest that tight glycemic control may slow the progression of neuropathy in some patients with T2D.[24] However, rapid lowering of blood sugar levels with insulin therapy has been associated with early worsening of retinopathy,[25] and higher rates of retinopathy complications have been reported with the GLP-1 RAs semaglutide[26] and liraglutide.[27] A beneficial effect on CV outcomes has been shown in long-term studies, in which intensive therapy resulted in a lower risk of death from CV causes.[28,29] However, intensive therapy was reported to lead to an increase in overall mortality rate and CV deaths in a study including an older, higher risk population with established CV disease or additional CV risk factors (eg, evidence of significant atherosclerosis, or at least 2 additional risk factors such as dyslipidemia, hypertension, smoking, and obesity).[30] The reason for this finding is unclear and does not seem to be explained by factors such as rate of reduction of A_{1c} to target levels, the incidence of severe hypoglycemia, weight gain, or insulin dose.[31] However, such data suggest that the potential risks of intensive glycemic control may outweigh its benefits in


At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:
A1C is <9.0%: consider Monotherapy
A1C is ≥ :9.0%: consider Dual Therapy
A1C is ≥10.0%, blood glucose is ≥300 mg/dL, or patient is markedly symptomatic: consider Combination Injectable Therapy
Monotherapy
Lifestyle Management + Metformin
Initiate metformin therapy if no contraindications[a]
A1C at target after 3 months of monotherapy?
Yes: – Monitor A1C every 3–6 months
No: – Assess medication-taking behavior – Consider Dual Therapy
Dual Therapy
Lifestyle Management + Metformin + Additional Agent
ASCVD?
Yes: – Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality
No: – Add second agent after consideration of drug-specific effects and patient factors
A1C at target after 3 months of dual therapy?
Yes: – Monitor A1C every 3–6 months
No: – Assess medication-taking behavior – Consider Triple Therapy
Triple Therapy
Lifestyle Management + Metformin + 2 Additional Agents
Add 3rd agent based on drug-specific effects and patient factors[b]
A1C at target after 3 months of triple therapy?
Yes: – Monitor A1C every 3–6 months
No: – Assess medication-taking behavior – Consider Combination Injectable Therapy
Combination Injectable Therapy

particularly vulnerable higher risk patients. Reflecting this possibility, treatment guidelines recommend that less stringent A_{1c} targets be considered for patients with some risk factors, including issues such as advanced atherosclerosis and other comorbidities (Fig. 2).[5–7,32]

Metformin is the recommended first-line option for most patients with T2D, generally followed by an oral antidiabetes drug (OAD) (Figs. 3 and 4).[5–7,33] Table I summarizes the characteristics of the medications commonly used to treat T2D.[5,26,27,34–36] The choice of second-line treatment will depend on multiple factors, including CV risk, vulnerability to hypoglycemia, and the extent of hyperglycemia. In all cases, however, treatment decisions must take a patient-centered approach that acknowledges multimorbidity, benefit and risk of treatments, and patient preference.[37]

It is not uncommon for patients to present at diagnosis with a significantly elevated A_{1c} level. In a prospective study of >7000 patients, mean A_{1c} level before the start of monotherapy was 9.6%.[13] However, despite this widespread elevated A_{1c} level, clinical inertia is a common problem, with patients and physicians alike often being reluctant to initiate injectable therapies. This reluctance can result in patients having suboptimal glycemic control for years at a time.[38] A study assessing the probability of achieving glycemic goals with oral monotherapy within the first year of treatment found that only 19%–24% of patients with T2D in the highest baseline A_{1c} category achieved A_{1c} levels <7.0% in the first year of treatment, compared with 86%–88% of those in the lowest baseline A_{1c} category.[39] Therefore, patients who present with extremely high A_{1c} levels (>9%–11.0%) and symptoms of hyperglycemia (eg, polyuria, polydipsia) are unlikely to achieve adequate glycemic control with metformin monotherapy. Patients with A_{1c} levels >9.0% are recommended treatment with GLP-1 RA or sodium glucose cotransporter 2 (SGLT2) inhibitors; those with A_{1c} levels >11.0%, symptoms of hyperglycemia, or evidence of ongoing catabolism should be considered for immediate insulin therapy. Subsequently, the addition of a GLP-1 RA, or switching to a fixed-ratio combination (FRC) of basal insulin and a GLP-1 RA, can result in lower insulin dosage requirements and greater glycemic control (Figs. 3 and 4).[5,6] A_{1c} goals should be set within the context of individual patient characteristics, including disease duration, life expectancy, relevant comorbidities, established vascular complications, and the degree to which a patient is at risk for hypoglycemia or other drug-related adverse effects (Fig. 2).[6,7,32]

KEY PRINCIPLE: ADVANCE THERAPY TO CONTROL HYPERGLYCEMIA

As previously mentioned, physician or patient inertia often causes a delay in treatment escalation. Close follow-up is needed, but often overlooked, for patients initiating basal insulin therapy or intensifying treatment. A treatment management plan should be in place, including assessment of treatment response at least every 3 months, and more often in patients in whom titration requirements necessitate frequent follow-up or in whom diabetes self-management and support are ongoing.[5–7,37] Facilitation of adherence should be a key part of any patient-centered treatment plan, with factors such as perceptions regarding treatment efficacy, fear of hypoglycemia, and other adverse effects of medication considered and addressed as part of follow-up.[37]

Advancing therapy most often includes adding a second or third OAD initially. Other options are to add an injectable GLP-1 RA, particularly in cases in which CV benefit is a priority, or, where appropriate, initiating therapy with basal insulin (Figs. 3 and 4).[5–7,37] Current guideline recommendations suggest initiating injectable therapy with a GLP-1 RA ahead of insulin in most cases.[37] In a network meta-analysis of clinical trials, the addition of insulin or GLP-1

Fig. 3. American Diabetes Association algorithm for initiating and advancing therapy for type 2 diabetes. [a]If patient does not tolerate or has contraindications to metformin, consider agents from another class. [b]Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors should not be prescribed in combination. If a patient with atherosclerotic cardiovascular disease (ASCVD) is not yet on an agent with evidence of cardiovascular risk reduction, consider adding. A1C = glycosylated hemoglobin. Reproduced from ADA 2018[5] with permission from ADA ©2018.

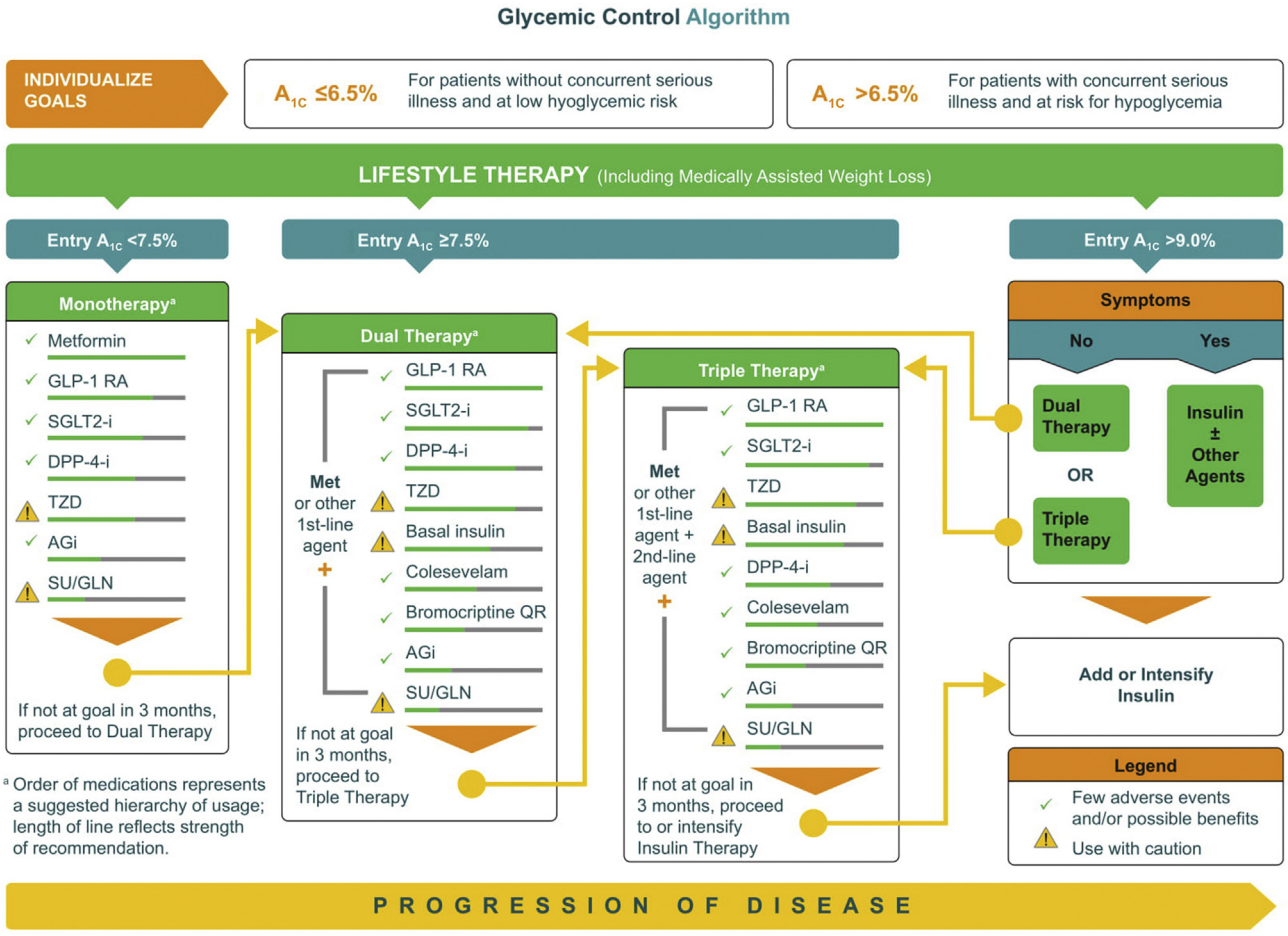


Fig. 4. American Association of Clinical Endocrinologists algorithm for initiating and advancing therapy for type 2 diabetes. A1C = glycosylated hemoglobin; AGi = alpha-glucosidase inhibitor; DPP-4-i = dipeptidyl peptidase-4 inhibitor; GLN = glinide; GLP-1 RA = glucagon-like peptide-1 receptor agonist; Met = metformin; SGLT2-i = sodium glucose cotransporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione. Reproduced from Garber et al[6] with permission from AACE ©2018.

RAs to metformin resulted in similar and superior A_{1c} reductions versus those obtained with the addition of oral agents (sulfonylureas, glinides, thiazolidinediones, α-glucosidase inhibitors, and dipeptidyl peptidase-4 [DPP-4] inhibitors).[40] The addition of basal insulin was associated with a greater risk of hypoglycemia and weight gain than observed with the thiazolidinediones, DPP-4 inhibitors, and GLP-1 RAs but a lower risk of hypoglycemia and weight gain than observed with sulfonylureas, glinides, or biphasic insulin; GLP-1 RAs did not increase the risk of hypoglycemia (vs placebo) and were associated with a significant decrease in body weight.[40] Combining drugs with different mechanisms of action, and consideration of hypoglycemia risk, potential for weight gain, complexity of the regimen, cost, and CV effects—in addition to gaining glycemic control—are important factors in decision-making.

Initiating basal insulin therapy is a recommended option for patients with T2D whose A_{1c} goals are not reached after 3 months on existing therapy[5–7] or who have significantly elevated A_{1c} levels (>11.0%), symptoms of hyperglycemia, or evidence of

Table I. Characteristics of commonly used medications for the treatment of type 2 diabetes.

Class	Physiologic Action	Advantages	Disadvantages	Administration
Biguanide (metformin)	Decrease hepatic glucose production	• Long experience • Low hypoglycemia risk • Relatively high A_{1c} reduction • Reduce CV events • Weight-neutral	• GI side effects • Vitamin B12 deficiency • Contraindicated: eGFR <30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration • Rare: lactic acidosis	Oral
Sulfonylureas	Increase insulin secretion	• Long experience • Reduce microvascular risk • Relatively higher A_{1c} reduction	• Hypoglycemia • Weight increase	Oral
TZDs	Increase insulin sensitivity	• Rare hypoglycemia • Relatively higher A_{1c} reduction • Durability • Reduce TG levels • May reduce CVD events	• Weight increase • Edema/HF • Bone fractures • Increase LDL-C levels • Pioglitazone contraindicated for bladder cancer	Oral
DPP-4 inhibitors	Glucose-dependent increase in insulin secretion and decrease in glucagon secretion	• Rare hypoglycemia • Well tolerated • Weight-neutral	• Angioedema/urticaria/ other immune-mediated dermatologic effects • Has been associated with pancreatitis, however no causal relationship has been established • Saxagliptin: increase HF	Oral
SGLT2 inhibitors	Block glucose reabsorption in kidney, increase glucosuria	• Rare hypoglycemia • Weight reduction • BP reduction • Empagliflozin: decreased CVD event rate and mortality (patients with preexisting CVD) • Canagliflozin: reduced risk of CV events	• Mycotic or bacterial genitourinary infections • Polyuria • Volume depletion • Increase LDL-C • Transient creatinine increase • Euglycemic DKA, urinary tract infections leading to urosepsis	Oral
GLP-1 receptor agonists	Glucose-dependent increase in insulin secretion and decrease in glucagon	• Rare hypoglycemia • Weight reduction • PPG reduction • Improve some CV risk factors • CVD events: benefit with liraglutide; no increase	• GI adverse events (may be transient) • Increase heart rate • May cause acute pancreatitis • Training requirements	Injected (BID, once daily, once weekly depending on agent)

Table I. (*Continued*)

Class	Physiologic Action	Advantages	Disadvantages	Administration
	secretion Slow gastric emptying Increase satiety	with lixisenatide or exenatide	• C-cell hyperplasia/ medullary thyroid tumors (animals)	
Insulins • Basal insulin • Prandial insulins	Increase glucose disposal Decrease hepatic glucose production Suppress ketogenesis	• Nearly universal response • Unlimited efficacy (limiting factor: hypoglycemia) • Lower microvascular risk • CV events: neutral effect with glargine or degludec	• Hypoglycemia • Weight gain • Training requirements • Patient/provider reluctance	Injected once daily (basal insulin) or 1 to 3 times daily (prandial insulin)

BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; A_{1c} = glycosylated hemoglobin; HF = heart failure; PPG = postprandial glucose; SGLT2 = sodium glucose cotransporter 2; TG = triglyceride; TZDs = thiazolidinediones.
Credit: American Diabetes Association[5] (modified); Marso et al[26,27,34]; ORIGIN[35]; Pfeffer et al.[36]

catabolism such as weight loss.[37] Basal insulin options include the first-generation analogues insulin detemir and insulin glargine 100 U/mL (Gla-100) and the newer second-generation analogues insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 or 200 U/mL. In general, basal insulin analogues are preferred to the older intermediate-acting neutral protamine Hagedorn (NPH) insulin.[5,6] Basal insulin analogues have the advantage of a more even pharmacokinetic and pharmacodynamic profile compared with NPH,[6] which results in a more consistent insulin action and a lower risk for hypoglycemia.[5,6]

Patients who are not at their A_{1c} goal but who have a sufficiently controlled fasting plasma glucose level require intervention to control postprandial glucose levels. Certain treatments have pronounced effects on postprandial hyperglycemia, including prandial insulin, glinides, and, to a lesser extent, DPP-4 or SGLT2 inhibitors.[41,42] Shorter acting GLP-1 RAs such as exenatide BID and lixisenatide once daily also have pronounced effects on postprandial hyperglycemia; however, longer acting GLP-1 RAs such as liraglutide once daily, dulaglutide once weekly, and semaglutide once weekly also have an impact.[43] For those patients taking basal insulin, intensifying therapy with prandial insulin can mean the addition of 1–3 injections before meals. Premixed insulins combine basal and prandial components in a single injection and are usually used BID, before the 2 largest meals.[44] Premixed insulins deliver additional reductions in A_{1c} and postprandial glucose levels compared with basal insulin but with a higher risk for hypoglycemia and less flexibility to adjust the component individual insulin doses. Advantages compared with basal plus prandial regimens include less complexity and reduced weight gain.[44] They are most appropriate for patients with very regular routines or those who can derive more benefit from the simplified regimen than from dose flexibility. Premixed insulins do not mimic physiologic insulin secretion and are therefore usually a less desirable option.

Alternatively to prandial insulin, addition of a GLP-1 RA should be considered. GLP-1 RAs also act on prandial glucose and have been shown to provide effective control, with A_{1c} reductions similar to or greater than those achieved with prandial insulin.[44–47] Adding a GLP-1 RA to basal insulin generally results in greater reductions in A_{1c} levels than are observed with placebo[48] and, compared with a prandial insulin,

achieves glycemic goals with lower hypoglycemia risk and weight loss (versus weight gain).[46,47,49] FRCs of basal insulin and a GLP-1 RA, similar to premixed insulins, can provide basal and prandial coverage in 1 daily injection. Those currently available are Gla-100 plus lixisenatide and insulin degludec 100 U/mL plus liraglutide; each is approved for patients whose disease is inadequately controlled on basal insulin or GLP-1 RA alone.[50,51] FRCs have a number of advantages that should be considered as part of a patient-centered treatment plan.[37] These include greater A_{1c} reductions than either of their components alone, without increasing hypoglycemia versus basal insulin, and mitigation of insulin-associated weight gain as well as GLP-1 RA-associated gastrointestinal (GI) side effects.[52–55] With weight loss, fewer GI effects, low hypoglycemia risk, and 1 daily injection, FRCs offer an effective alternative to premixed insulins or complex, multiple-OAD treatment regimens.

OTHER CONSIDERATIONS IN T2D TREATMENT CHOICE

Minimizing hypoglycemia risk is a key principle of T2D management;[5] hypoglycemia intimidates patients and physicians, limits effective titration of basal insulin and treatment intensification, and, if unchecked, increases morbidity and mortality.[16,56,57] Although a 5-year follow-up study of patients with T2D confirmed that Gla-100 provides sustained reductions in hypoglycemia compared with NPH,[58] newer basal insulin analogues, such as Gla-300 and insulin degludec, further reduce hypoglycemia risk, especially at night, compared with Gla-100, while delivering similar reductions in A_{1c} level.[59–66] Glycemic control and lower rates of hypoglycemia are durable at 52 weeks' follow-up.[65,66] Insulin degludec 200 U/mL and Gla-300 each provide a higher dose of insulin in the same injection volume as Gla-100; either is appropriate for any patient who requires basal insulin therapy. Gla-300 provides a more even steady-state pharmacokinetic and pharmacodynamic profile than Gla-100 and insulin degludec 100 U/mL.[67–69] Both insulin degludec and Gla-300 have flat, non-peaking action profiles; Gla-300 has a duration of action of up to 36 h, and insulin degludec has a duration of action of up to 42 h.[67–72] The recent BRIGHT study showed that, in patients with insulin-naive T2D inadequately controlled with oral antihyperglycemic drugs ± GLP-1 RAs, Gla-300 and insulin degludec 100 U/mL provide similar glycemic control.[73] However, Gla-300 was associated with a lower rate of hypoglycemia, particularly during the initial 12-week titration period, during which the overall daily rate of hypoglycemia was 23% lower and nocturnal hypoglycemia 35% lower than with insulin degludec.[74]

Another consideration when escalating therapy is the effect on CV risk. Patients with T2D are at high risk of CV complications, and most have multiple CV risk factors in addition to diabetes.[75] In 2008, the US Food and Drug Administration added a requirement that new antihyperglycemic medications brought to market also demonstrate CV safety. To date, 9 such trials covering DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 RAs have been completed, all of which have shown no increase in risk of major CV events and some of which have shown CV benefits of treatment compared with placebo.[76] In recognition of these data, recent treatment guidelines recommend the addition of an agent with evidence of CV risk reduction, in particular a GLP-1 RA or SGLT2 inhibitor, in patients with atherosclerotic CV disease or heart failure when advancing to dual therapy and beyond in patients with T2D.[5] Although older classes of drugs, including metformin and sulfonylureas, were never studied for specific CV end points, these older drugs have accumulated real-world experience supporting their safety and are cost-effective options for patients who are unable to afford, or do not have insurance coverage for, the newer agents.[77,78]

CHALLENGES IN PRIMARY CARE

Primary care clinicians face many challenges in ensuring that patients with T2D advance their therapy as needed to retain glycemic control. A major factor causing delays in initiation or intensification of treatment is clinical inertia of physicians, patients, and the health care system.

It is not uncommon for clinicians to encounter resistance to a change in treatment from their patients. It has been suggested that a range of patient-related barriers account for ~30% of the principal factors contributing to clinical inertia.[79] These patient barriers depend on a variety of factors, such as health literacy, costs, number of medications, trust in their physician, and communication and time with their physician.

Table II. Strategies to address patient concerns about using injectable therapy.

Barrier	Strategy
Belief that disease has worsened	• Explain progressive nature of type 2 diabetes; educate patients starting at diagnosis
Injection-related anxiety	• Demonstrate the needles and injection device(s) they will be using for insulin/GLP-1 RA/FRC and for self-monitoring • Discuss how needle design improves comfort • Instruct on proper injection technique • Allow supervised injection rehearsals
Perception that insulin is ineffective	• Assure patients that therapy will improve symptoms and make them feel better
Fear of weight gain	• Use once-daily insulin analogues to minimize weight gain • Use insulin in combination with metformin • Explain the potential benefits of GLP-1 RAs and GLP-1 RA/basal insulin FRC in terms of mitigation of weight gain • Discuss diet and daily exercise to moderate/prevent weight gain
Fear of hypoglycemia	• Explain low incidence of severe hypoglycemia with basal insulin analogues, GLP-1 RAs, and with FRC • Use once-daily insulin analogues to minimize hypoglycemia risk • Consider intensification of insulin therapy with agents associated with low risk of hypoglycemia
Fear of injection-related pain	• Identify past experiences with injections • Identify perceptions about injections • Deep breathing or forceful exhalation during injection • Decrease number of injections with FRC
Monitoring	• Assess patient response to prescribed insulin and/or GLP-1 RA therapy • Provide follow-up education and counseling as needed

FRC = fixed-ratio combination; GLP-1 RA = glucagon-like peptide 1 receptor agonist.
Adapted from: Kruger et al[15]; Peyrot et al.[84].

Diabetes distress, which arises in response to the pressures of living with diabetes, can be a particular problem when treatment targets are not being met and a change in therapy is needed.[80] A specific "insulin distress" linked to a perceived inability to cope with the requirements of insulin therapy has also been described.[81] It is recommended that patients be carefully monitored during this time and any issues relating to such distress be explored and addressed. Counseling and education should be provided where required, in particular "coping therapy" based on the principles of strengthening self-care skills, optimizing coping skills, minimizing change-related discomfort, and making use of external support.[80,81]

Common objections expressed by patients with T2D who are moving on to injectable therapy include fear of injections, of weight gain, of negative effects on quality of life, and of the illness becoming more severe; they may lack confidence in their ability to handle the regimen and may believe that the need for insulin represents a failure on their part. Several strategies are available that can help in overcoming patients' objections to injectable therapies (Table II).[12,15,82–84]

Although patients express a preference for less frequent injections,[85] clinicians often overestimate the degree to which fear of injection pain concerns patients.[12] Discussing patients' attitudes toward their disease, reviewing or demonstrating the injection device they will use with mock insulin injections, and

Table III. Address patient concerns regarding their treatment or disease progression.

Open-ended questions to explore patients' barriers to insulin therapy:

- How satisfied are you with your current diabetes therapy?
- How do you think insulin can help with your diabetes?
- Who do you know who has used insulin, and what was their experience?
- What is your greatest concern about using insulin?
- How confident are you that you can inject insulin on a regular basis?
- What obstacles do you think will keep you from taking insulin?
- What information or support do you need to be willing to take insulin injections?

Adapted from Kruger et al.[15]

explaining the benefits of their treatment can help to overcome these fears.[15]

Social concerns are another aspect to consider. Fear of social stigma often leads to nonadherence and can negatively affect treatment outcomes. Physicians should discuss these concerns with their patients and help them to find solutions to minimize the impact of the treatment on the patients' daily routines and social lives.[83,86] Such concerns, related to anxiety about their treatment or disease progression, are best explored with open-ended questions as shown in Table III.[15,82] The examples given are focused on insulin therapy, but similar questions can be asked when intensifying therapy by the addition of other injectables.

An important part in helping patients overcome their barriers to advancing therapy is educating them on the progressive nature of their disease, thus preparing them that therapy intensification is expected and avoiding the impression that progression to insulin therapy represents a failure on the patient's part.[12,84] Almost one half of patients in the DAWN (Diabetes Attitudes, Wishes, and Needs) study expressed the belief that beginning insulin meant they had failed to follow previous treatment properly; furthermore, this was the negative belief that was most associated with unwillingness to begin insulin therapy.[17] Explaining to patients early on that their disease is progressive by nature, and that the need to change or add to their therapy, including starting insulin, will likely occur in the years ahead, can minimize patient objections when such change is required. Clinicians must emphasize that adjusting therapy is not a sign of personal failure.

If patients are to succeed, clinicians also must confront and overcome their own barriers to advancing therapy. These include doubts that patients will comply or be able to accept the discomfort of injections.[12,15,82] For example, despite guideline recommendations that self-titration has been shown to be an effective tool, many physicians prefer to manage titration due to a lack of confidence in their patients' ability to adjust their dose correctly; compliance, or lack thereof, is also often cited as a potential issue, along with a lack of involvement and motivation.[5,86] Interestingly, >80% of US patients expressed some confidence that they would be able to titrate their insulin dose correctly. However, the same study reported that 42% of the patients were not aware that titration was needed, suggesting that there is a need for improved patient education.[86] When initiating insulin therapy, timely follow-up to assess titration is essential. An increased risk of hypoglycemia is a concern not only to patients but also to physicians.[16] Direct discussion with patients regarding the potential risk of hypoglycemia, how to prevent it, how to recognize the symptoms, and how to treat it might help to reduce patients' fears.

Clinicians' inattention to or lack of engagement with patient concerns are key reasons for poor adherence to injected therapies.[87] As such, good communication between physicians and their patients is a key element in reducing clinical inertia. When asked, patients express a strong interest in education about their disease and their own role in disease management for healthy outcomes;[82] however, the lack of relevant knowledge, tools, and time required to provide education is cited by clinicians as a barrier to prescribing insulin or other injected therapy.[84,88] Diabetes educators are available to provide invaluable assistance with issues from insulin injection techniques to nutrition advice, and should be part of the treatment team as much as possible. In addition, developing treatment strategies and setting goals and expectations on how to manage patients' disease,

together with patient education, could help both patients and physicians to overcome some of the barriers and minimize clinical inertia, while increasing patient adherence and treatment outcomes. A variety of other strategies have shown promise in reducing clinical inertia on the part of physicians, such as monitoring and providing feedback to physicians on the quality of their patient care, more frequent office visits, clinical-decision support, and tools for visit resolution and accountability.[89]

CONCLUSIONS

Due to the progressive nature of T2D, the need to advance therapy over time is a reality for most patients. Treatment guidelines recommend individualized treatment targets based on patient characteristics such as CV risk and other comorbidities. Better outcomes can be achieved if clinicians avoid clinical inertia in advancing therapy to achieve such targets across their patients' lifetimes. Injectable agents represent important options to advance therapy and reduce hyperglycemia, but often meet resistance from patients and clinicians. Basal insulins that provide effective glycemic control with low hypoglycemia risk afford greater comfort and more dosing flexibility. GLP-1 RAs alone or combined with basal insulin provide good glycemic control with weight loss or less weight gain, low hypoglycemia risk, and potential beneficial CV effects. FRCs of basal insulin and a GLP-1 RA provide greater A_{1c} reductions than either of their components alone and mitigate weight gain and GI side effects. To improve patient outcomes, clinicians must be willing to address patient concerns and implement appropriate therapies in a timely manner.

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CONFLICTS OF INTEREST

Dr. Cavaiola is a consultant for Dexcom, Novo Nordisk, Sanofi, and Senseonics Dr. Reid is a speaker/consultant for AstraZeneca, Intarcia, Janssen, Lilly, Novo Nordisk, and sanofi-aventis. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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