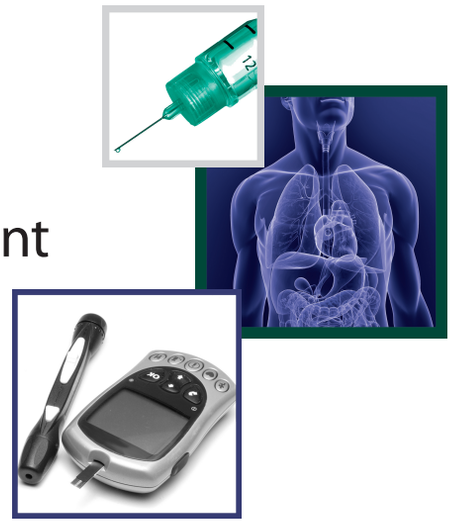

International Diabetes Center Treatment of Type 2 Diabetes Glucose Algorithm

Gregg Simonson[†1], Robert Cuddihy[1], Diane Reader[1] & Richard Bergenstal[1]

Practice Points

- Establish A1C and self-monitored blood glucose targets with the patient and treat-to-target.
- If glycemic targets are not achieved or no significant improvement is observed within 3 months, advance therapy by titrating the dose or adding additional medication.
- Referral for diabetes education and medical nutrition and activity therapy at diagnosis, ongoing and when glucose is poorly controlled, is critical; all therapies work better when patients follow their self-management plan.
- Metformin should be considered as a first-line therapy owing to its efficacy, durability, weight neutrality, low cost and reduced risk of hypoglycemia.
- Use combination therapy early in the Type 2 diabetes treatment paradigm and consider two-drug therapy if baseline A1C is 9–11%.
- Glucagon-like peptide-1 agonists are the only therapies that have a demonstrated effect on weight loss.
- Insulin is a very effective therapy and multidose insulin therapy should be considered if A1C is greater than 11% to overcome glucotoxicity.
- When starting multidose insulin, discontinue sulfonylurea, start or maintain metformin, consider maintaining dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 agonists if a positive response to the drug is observed, and discontinue thiazolidinedione in most cases to avoid weight gain.
- Remember that patients not achieving targets may benefit from a psychosocial evaluation, which may include screening for depression, anxiety and low health literacy or numeracy.

SUMMARY With the growing worldwide diabetes epidemic, the management of individuals with Type 2 diabetes (T2D) will, out of necessity, be undertaken more by primary-care health providers and less by subspecialist diabetologists. To overcome the barriers to effective management of T2D, we will need to address the issue of clinical inertia by providing healthcare professionals with pragmatic evidence-based algorithms. The International Diabetes Center (MN, USA) has created an algorithm for T2D, which is customizable to local conditions and fosters discussion between the patient and provider of the risks and benefits

[1]International Diabetes Center at Park Nicollet, 3800 Park Nicollet Blvd, Minneapolis, MN 55416, USA
[†]Author for correspondence: Tel.: +1 952 993 3830; Fax: +1 952 993 1302; gregg.simonson@parknicollet.com

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of the different therapeutic options. Using clinical evidence coupled with clinical experience, it establishes a glycemic target-driven systematic, multidiscipline team approach to initiate and advance T2D therapies by addressing the underlying pathophysiological defects associated with T2D.

With the continually growing epidemic of Type 2 diabetes (T2D) and the ongoing limited number of endocrinologists or diabetes specialists, more patients are inevitably being managed either exclusively or almost solely by primary-care or general practitioners. These practitioners must address the multiple competing demands placed upon them in their dealings with patients in whom diabetes is likely to be one of many active medical issues. There is clearly a need for evidence-based tools incorporating expert advice to aid the general practitioner in counseling their patients and enabling appropriate clinical decision making in terms of diabetes therapy. Clinical inertia in advancing and titrating diabetes-related therapies remains a major barrier to achieving good glycemic control [1–3]. Glycemic management algorithms would hopefully aid in overcoming clinical inertia to improve overall glycemic control [2].

All algorithmic approaches can only serve as a guideline, and not a mandate, to the treating clinician. The provider will certainly understand the important features and nuances of their specific patient's case (i.e., financial resources, drug allergies or intolerances, patient preferences, adherence to a regimen and treatment goals), which greatly impact the appropriate choice of therapy. The algorithm should be descriptive rather than proscriptive to aid the treating clinician in reaching an agreed-upon course of action with their patient. No one algorithm is likely to be equally effective in different locales around the world, as local conditions such as resources, access to healthcare and medications, and even the genotypic and phenotypic makeup of discrete populations vary widely. Therefore, one important feature of any algorithmic approach would be its ability to be customized to meet 'the local conditions on the ground' of where this tool is intended to be used.

The International Diabetes Center (IDC) at Park Nicollet Health System, MN, USA, has created a series of treatment algorithms for the management of diabetes based on the latest diabetes research, clinical evidence and expert opinion. The intent of these guidelines is to provide a means for the primary-care health professional to select the most appropriate therapy and to advance therapy if metabolic targets are not achieved. Algorithms can also serve as a valuable communication tool between diabetes educators, dietitians, other members of the diabetes team and the medical provider. The IDC Treatment of T2D Glycemic Control Algorithm is shown in **Figure 1**. The IDC was one of the early pioneers in the USA, broadly developing, teaching and applying an evidence-based algorithmic approach to the treatment of T2D for primary care through their Staged Diabetes Management® (SDM) program, with the publication of clinical *Decision Paths* for Type 1, Type 2 and gestational diabetes in 1995, shortly following the completion of the landmark Diabetes Complication and Control (DCCT) trial [4]. SDM was later published in textbook form by the IDC as a first edition in 2004, with later editions published by John Wiley and Sons [5]. In recent years, other national organizations, such as the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE), have established consensus panels to create guidelines for managing T2D [6,7]. Editorials have been written espousing the benefits and issues associated with diabetes guidelines [8,9]. The IDC's approach to the creation of its glucose algorithm matches the clinical evidence, with clinical considerations to drive the selection of therapy that is most appropriate for the individual patient **(Figure 1 & Box 1)**.

Glycemic targets

Critical to the IDC algorithm is the establishment of glycemic targets, as this clearly defines with both the patient and their diabetes team what the goal of therapy is. National organizations such as the ADA and AACE have also established glycemic targets [6,10]. While the glycemic targets from different organizations are all slightly different, they do share some common themes **(Table 1)**. For example, they all have a postmeal self-monitoring blood glucose target reflecting the contribution of prandial blood glucose in the level of hemoglobin A_{1c} (A1C). Work by Monnier and colleagues revealed that postmeal blood glucose is a larger contributor to the A1C value in the lowest quintile (closer to target) than A1C in the highest quintile where

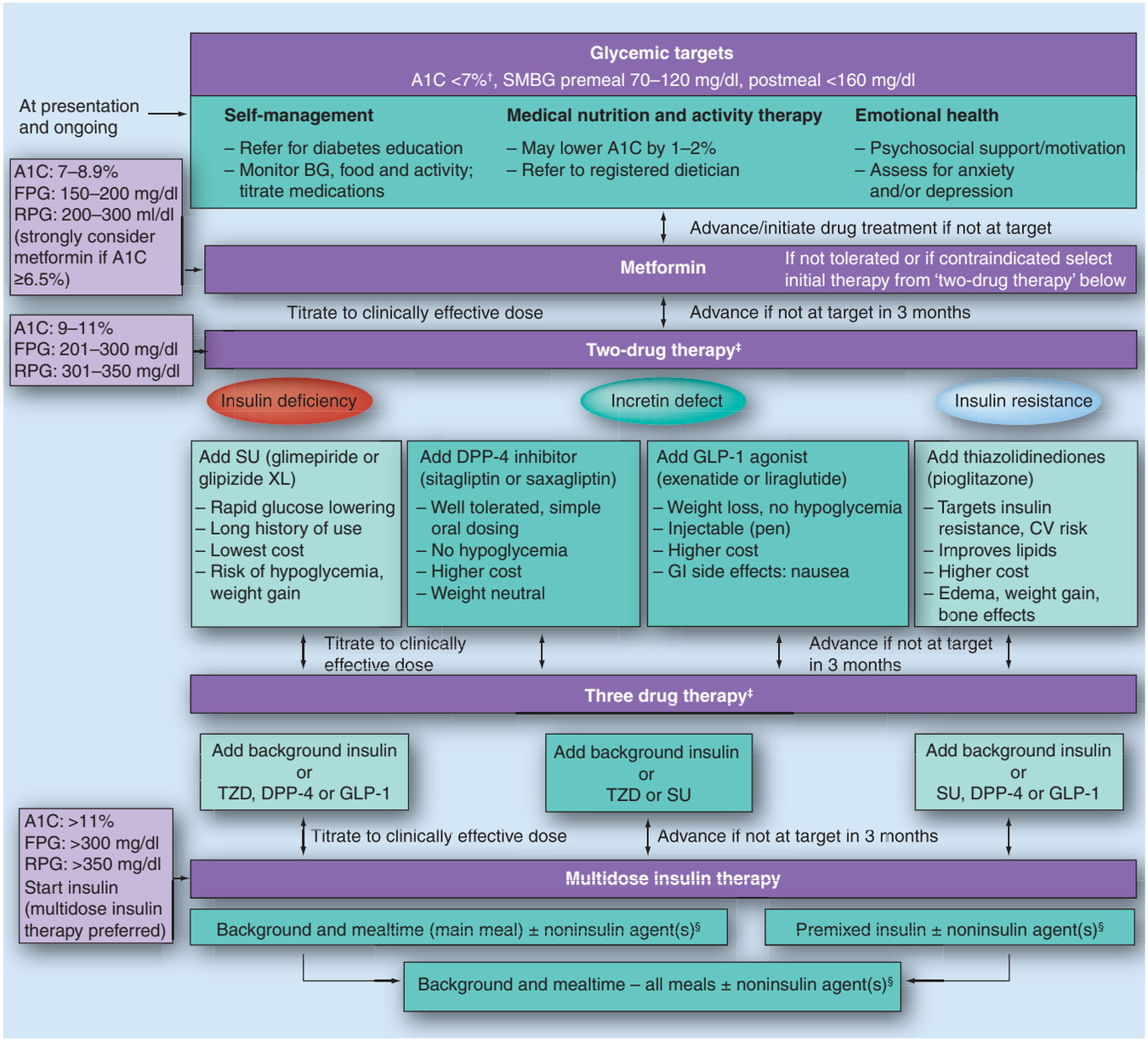

Figure 1. International Diabetes Center treatment of Type 2 diabetes: glycemic control algorithm.

†A1C <7% for many patients (particularly to prevent progression of microvascular disease); consider target <8% for those with major medical comorbidities, hypoglycemic unawareness, the frail elderly or those whose therapy has been significantly intensified without seeing an improvement in glycemic control.

‡Other noninsulin therapies may be considered, see clinical considerations.

§Discontinue sulfonylureas, recommend adding or maintaining metformin, consider maintaining DPP-4 inhibitor or GLP-1 agonist if positive response to drug; discontinue thiazolidinedione in most cases.

A1C: Hemoglobin A_{1c}; BG: Blood glucose; CV: Cardiovascular; DPP-4: Dipeptidyl peptidase-4; FPG: Fasting plasma glucose; GI: Gastrointestinal; GLP-1: Glucagon-like peptide-1; RPG: Random plasma glucose; SMBG: Self-monitored blood glucose; SU: Sulfonylurea; TZD: Thiazolidinedione.

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high fasting blood glucose was the greatest contributor [11]. The IDC is similar to the ADA in that it recommends an A1C lower than 7% for many patients while working to minimize the risk for severe hypoglycemia. Higher A1C targets (e.g., <8%) may be appropriate for patients

Box 1. International Diabetes Center treatment of Type 2 diabetes: clinical considerations.

- Check kidney and liver function prior to initiation of noninsulin therapies
- Pioglitazone is recommended over rosiglitazone owing to concerns of increased cardiovascular risk with rosiglitazone
- Long-acting background (basal) insulins detemir and glargine reduce the risk of nocturnal hypoglycemia compared with intermediate-acting neutral protamine Hagedorn insulin; some patients may benefit from b.i.d. dosing of long-acting insulin
- If a clinically stable patient with an A1C level over 11% is consuming an excessive amount of sweetened beverages, discontinue beverages and consider starting noninsulin agents and re-evaluate the need for insulin in 1–2 weeks
- Pramlintide may be added to mealtime insulin
- Background and mealtime insulin regimen is the most physiological and flexible regimen
- Focus on modest weight loss of 5–7% total bodyweight for patients with a BMI of over 26
- General nutrition recommendations include elimination of sweetened beverages and eating a minimum of three meals per day with each containing approximately three carbohydrate choices (45 gm/meal)
- Recommend goal of 150 min per week of physical activity, for example, 30 min five days per week
- Consider referral to a psychologist or social worker if A1C is persistently elevated, to address non-medical barriers to glycemic control
- If the patient is treated with metformin and FPG is significantly elevated, consider adding background insulin
- Other noninsulin therapies to consider
  - α-glucosidase inhibitor if A1C level is close to the target and postmeal glucose is elevated due to excessive carbohydrate intake
  - Nateglinide or repaglinide if postmeal hyperglycemia occurs and there is a need for a flexible mealtime dosing schedule
  - Colesevelam if A1C is close to the target and low-density lipoprotein levels remain above the target with the current statin therapy
  - Bromocriptine if A1C is close to target; works through CNS-mediated improvement in insulin sensitivity
- Self-management education includes understanding disease state, glucose monitoring, insulin injection and how to respond to daily glucose excursions

A1C: Hemoglobin A_{1c}; b.i.d.: Twice daily; FBG: Fasting plasma glucose.

with major medical comorbidities, hypoglycemic unawareness, the frail elderly or those whose therapy has been significantly intensified without seeing an improvement in glycemic control. The IDC realizes that patients who have recently been diagnosed with diabetes may well be able to safely achieve even tighter glycemic control. The AACE has the most aggressive A1C target of no more than 6.5%, based primarily on data from the UK Prospective Diabetes Study (UKPDS), showing no threshold of risk reduction for micro- and macro-vascular complications of diabetes [12]. After the report of increased mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in a cohort intensively treated with a A1C of 6.4% (targeting <6.0%), it became less clear what the target A1C for preventing cardiovascular disease should be, although a target of 7% still seems very logical, evidence based and safe for the majority of patients with T2D [13]. Further support for tighter glycemic control comes from recent analysis of ACCORD data showing that intensive blood glucose control prevents the onset of albuminuria and progression of retinopathy [14,15].

While A1C, fasting/premeal and postmeal glucose make up the primary glycemic targets, new technology such as continuous glucose monitoring allows us to learn more about glucose profiles, and the IDC envisions that targets will be expanded and personalized. For instance, establishing an optimal glycemic target (A1C target or self-monitoring blood glucose/continuous glucose monitoring target of the percentage of time spent in the target range) may be paired with an acceptable amount of mild or symptomatic hypoglycemia and tracking and trying to eliminate any severe hypoglycemia. In addition, measures of glucose variability and stability will likely be incorporated into glycemic targets in the future if outcome trials confirm their suspected impact on microvascular or macrovascular disease risk.

Self-management education, medical nutrition, activity therapy & emotional health

Diabetes self-management education is defined as the ongoing process of facilitating the knowledge, skill and ability necessary for diabetes self-care. Successful diabetes management is contingent upon many factors, including a patient's ability to understand the nature of the disease and how they can participate and enable the treatment plan. The IDC algorithm recommends referral to a diabetes education program for all people with diabetes at diagnosis, when medication changes are made and when a patient is struggling to improve glucose control.

Both group and individual education have been demonstrated to be equally effective [16]. Recent research has shown that patients who received self-management education had lower claim costs, lower inpatient admission rates and better compliance with diabetes medication [17]. It is recommended that clinicians refer the patients to a program that follows the National Standards for Diabetes Self-Management Education or International Diabetes Federation (IDF) educational guidelines, or to a Certified Diabetes Educator. Recognized programs or Certified Diabetes Educators can be found at [101], and for the IDF guidelines, see [102].

Nutrition therapy is often referred to as the cornerstone of diabetes management and there is substantial evidence supporting its effectiveness in T2D. The Diabetes Prevention Program (DPP) trial [18] and the Finnish Diabetes Prevention Program [19] have clearly demonstrated the marked benefits of successful lifestyle modification in reducing the risks of developing overt T2D in a high-risk population, with the DPP trial demonstrating that the effectiveness of successful lifestyle modification clearly trumps the benefit that can be derived by medication alone (i.e., metformin). Follow-up of participants in the DPP trial at 10 years post-randomization demonstrated that the cumulative impact of intensive lifestyle intervention is greater than that of metformin in preventing diabetes [20]. Medical nutrition therapy (MNT) can reduce A1C by 1–2 percentage points and in the newly diagnosed patient may lower A1C by 3 percentage points or more [21]. These outcomes are generally observed when registered dietitians provide MNT. The goals of MNT focus on achieving blood glucose, blood pressure and lipid targets while addressing the individual's needs and preferences as well as their willingness to change. Carbohydrates, including fruit, starch, milk and sugar, are the primary food substance that raises postprandial blood glucose levels; therefore, monitoring the total amount of carbohydrate intake is key to controlling glucose levels at each meal and snack. Carbohydrate counting is a method to quantify and manage carbohydrate intake; one carbohydrate choice contains approximately 15 g of carbohydrate, such as one slice of bread, a small piece of fruit or half a cup of ice cream. A typical food plan contains three to four carbohydrate choices (each ~15 g) or 45–60 g per meal. Monitoring and ongoing evaluation will determine if the food plan is appropriate (e.g., if it fits the patient's eating pattern, results in meeting metabolic goals and works with the action of diabetes medications). Some providers may educate their patients to utilize the glycemic index of specific foods (usually measured as the relative contribution to 2-h postprandial glycemic levels of specific foods as compared with a standard 50-g glucose load) when making appropriate food selection choices. However, this concept is not widely adopted or currently utilized within the USA. Controlling carbohydrate intake frequently results in weight reduction [16]. Research has shown that a modest weight reduction of 5–7% of bodyweight and an increase in physical activity to 150 min per week improves glucose control and prevents or delays the onset of diabetes [22,23]. The LOOK AHEAD trial involved intensive contact with a diabetes team with weekly visits for the first 6 months, slowly decreasing to twice-monthly contact (visit and telephone) by years 2–4 of the trial, but did demonstrate that it was possible for such an intervention to yield lifestyle changes producing sustained weight loss and improvements in glycemic control, fitness and cardiovascular risk in almost 60% of patients over 4 years [24].

Non-medical aspects, such as emotional health, support and literacy, are often overlooked. People with diabetes are at a much greater risk of depression, with an estimated prevalence of 15–20% [25]. Patients with depression are significantly less likely to engage in self-management activities such as carbohydrate counting, exercise and self-monitoring of blood glucose [26]. Even more common than depression is those with diabetes having anxiety about their condition, which may interfere with their diabetes management. A not uncommon scenario is a patient's A1C remaining in the greater than 9% range over several months to years despite the provision of a proper diabetes education and medication regimen. These individuals are likely to have psychological, financial or social barriers to improving their

Table 1. Glycemic targets.

	IDC	ADA	AACE
A1C	<7.0%	<7.0%	≤6.5%
Fasting/premeal BG	70–120 mg/dl	70–130 mg/dl	<110 mg/dl
2-h postmeal BG	<160 mg/dl	<180 mg/dl[†]	<140 mg/dl

[†]1–2 h after start of meal.
A1C: Hemoglobin A_{1c}; AACE: American Association of Clinical Endocrinologists; ADA: American Diabetes Association; BG: Blood glucose; IDC: International Diabetes Center.

glucose control, which often go unaddressed. Interestingly, in the ACCORD study, it was the population in the intensive glycemic control group with the highest A1Cs who failed to improve significantly and who suffered from the greatest rates of hypoglycemia and increased mortality [27]. Perhaps this outcome suggests that to continue to push 'aggressive' therapy in those individuals with cognitive or psychosocial barriers to improve glycemic control entails the greatest danger. Thus, the IDC algorithm stresses the need to assess for anxiety and/or depression. Moreover, the level of psychosocial support and motivation for engaging in self-management skills is a critical aspect of the treatment of T2D requiring ongoing assessment. The recent rise in popularity of the motivational interviewing techniques to better engage patients in their own self-care seeks to help address this important barrier. In addition, it is becoming clear that an evaluation for low health literacy and numeracy may help identify additional barriers that need to be understood or overcome to safely optimize glycemic control [28,29].

From the provider aspect, a critical feature built into the IDC algorithm to reduce clinical inertia is a 3-month timeline to advance therapy if A1C target is not achieved. The IDC's algorithm's outlining of salient pros and cons for each general medication class may serve to enable the patient–provider interaction and discussion surrounding advancing therapy, hopefully achieving greater patient investment in, and adherence to, the eventual decisions made to improve their diabetes control.

Metformin therapy

Metformin monotherapy is widely accepted as either a concurrent or the next therapeutic modality, following efforts at lifestyle modification. One reason is its long history of clinical use (over 50 years) and the assurance this brings that there are unlikely to be unknown safety issues associated with its use. In addition, its availability as an inexpensive generic drug and its properties, which include potent A1C lowering both as monotherapy and in combination with other agents, its potential inducement of initial weight loss and long-term weight neutrality, and the relative lack of hypoglycemia observed when used as monotherapy all contribute to its choice as a first-line therapy. Evidence of additional potential beneficial effects in terms of the metabolic syndrome and its demonstrated ability to prevent diabetes clinch metformin's place as a first-line therapy [23]. For example, as seen in a small cohort of obese individuals with T2D in the UKPDS, in those treated with metformin there was a statistically significant reduction in the event rate of myocardial infarction [30]. A recent publication provides additional evidence that initiating metformin soon after the diagnosis of diabetes while A1C is relatively low might preserve β-cell function, prolong the effectiveness of metformin and reduce the lifetime glycemic burden [31]. For all these reasons, metformin assumes its proper position in the IDC glycemic algorithm **(Figure 1)** as a recommended first-line therapy unless the patient is intolerant or has contraindications to its use.

One major concern regarding the use of metformin is the risk of lactic acidosis in those with renal impairment (serum creatinine >1.4 mg/dl in women and >1.5 mg/dl in men). Recent studies have shown that 'fear of lactic acidosis' is unfounded and is quite rare, and is in line with other established diabetes oral medications [32]. Much of the concern over lactic acidosis may stem from concern by association with the earlier biguanide phenformin, which was associated with a higher risk of lactic acidosis, and may be more due to underlying medical conditions rather than the medication itself [33]. Owing to this, metformin is increasingly being used in patients with moderate renal impairment, defined as stage 3 chronic kidney disease (estimated glomerular filtration rate: 30–59) but remains absolutely contraindicated in stage 4 and 5 (estimated glomerular filtration rate: <30) [34]. Metformin has also been demonstrated to reduce mortality in patients with heart failure [35]. Moreover, there is a growing accumulation of evidence that metformin therapy is not associated with an increased risk of malignancy and that it may in fact be associated with a decreased risk for malignancy [36,37]. If a patient were intolerant to metformin therapy or had a contraindication to its use, the health provider would be instructed to proceed down to the next level on the algorithm and to choose an agent from the 'two-drug therapy' row to be used as initial monotherapy.

Two-drug therapy

If glycemic targets are not achieved within 3 months, therapy should be advanced to further improve glycemic control and reduce the

patient's risks for long-term complications. In addition, if an individual's glycemic control is so poor that their initial A1C is 9–11%, fasting blood glucose is 201–300 mg/dl and/or random plasma glucose is 301–350 mg/dl, it is unlikely that metformin monotherapy coupled with MNT will be sufficient to allow most individuals to achieve their glycemic targets, and so two-drug therapy should be initiated.

The choice for two-drug therapy with metformin includes a host of noninsulin agents as well as insulin, although it is abundantly clear that both patients and their primary-care physicians rarely choose insulin this early in disease progression. To date, there is little evidence that proceeding directly to insulin after monotherapy failure has unique advantages over other therapies except for the fact that there is no limit to the ability of insulin to lower glucose, unlike oral or noninsulin injectables. We await the results of the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, likely to be available in 2012, which is evaluating cardiovascular outcomes in patients treated with insulin in the prediabetes stage or in patients with early T2D. An algorithm must recognize practicality and 'real-world' utility for it to have any hope of being adopted by the very audience it seeks to aid. This is an area where the IDC Glycemic Control Algorithm differs from the ADA–EASD consensus statement algorithm, which has a more conservative approach, most heavily weighing the maximum glucose-lowering effect and the least-expensive versus the most physiologic or patient preference-driven approach [7]. While the ADA–EASD consensus algorithm steers healthcare providers towards second-line treatment with either neutral protamine Hagedorn (NPH) insulin or a sulfonylurea, the IDC algorithm centers around recommending appropriate therapy based on weight, cost, hypoglycemia risk, side effects and underlying pathophysiology, in addition to the ability to lower the A1C. However, one fundamental difference of the IDC glycemic control algorithm is that it is designed to be customizable for different organizations or populations based upon local practice patterns, resources and specific features of the target population.

For example, the two-drug therapy row of the IDC algorithm includes sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists or thiazolidinediones (TZDs) but not meglitinides, α-glucosidase inhibitors or colesevelam, as does the AACE algorithm [6]. These medications are not commonly used for T2D management in the USA, owing to their having a lower efficacy regarding glycemic lowering, adherence issues due to frequent daily dosing and poor side-effect profiles. Interestingly, certain medications, such as α-glucosidase inhibitors, are occasionally added back to the customized algorithms in areas where they are in common use. We also sought to avoid overcrowding of the main algorithm, which by nature should be simple and easy to use, and to strike the appropriate balance between being overly directive versus providing too little subspecialty guidance to our primary-care colleagues. We sought to eliminate unnecessary cataloging of all potential choices, which are often of marginal value.

The IDC algorithm also provides a theoretical framework for choosing a second-line agent based on the chief underlying pathophysiologic process most evident in any particular patient (Figure 2). Thus, in an individual of healthy weight without any (or very few) features of the metabolic syndrome, relative insulin deficiency may be more prominent, and such an individual may respond better to insulin secretagogues such as a sulfonylurea, while in an obese individual with obvious prominent features of insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia and a fatty liver, one may favor an insulin sensitizer such as a TZD. In an individual where marked postprandial hyperglycemia

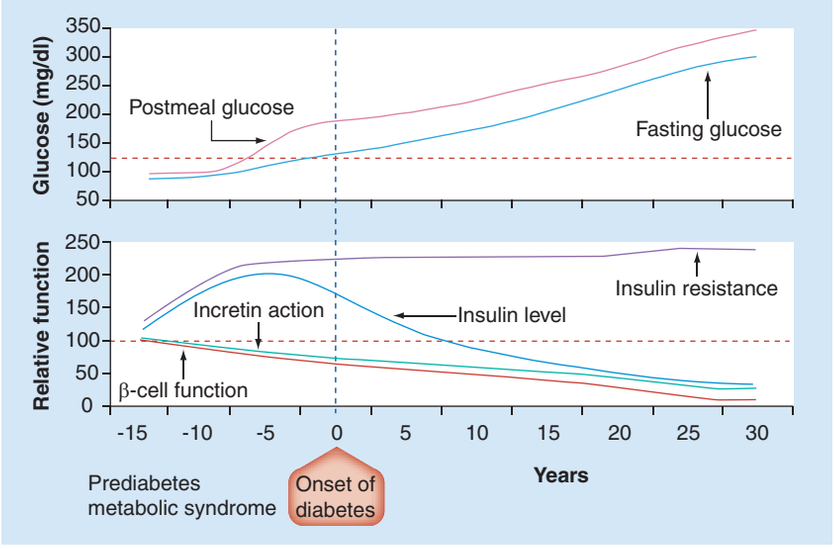

Figure 2. Natural history of Type 2 diabetes.
Adapted from [74] with permission from © International Diabetes Center (2010).

and poor appetite control with obesity are most prominent, perhaps therapy with an incretin-based agent might be expected to be most useful. Finally, for individuals at risk for, or with great fear of, hypoglycemia, the clinician may want to select one of the three agents in the IDC second drug list that do not cause hypoglycemia when used in combination with metformin (i.e., a DPP-4 inhibitor, GLP-1 agonist or TZD).

Starting from the left-hand side of the two-drug therapy section on the IDC algorithm, sulfonylurea-class glimepiride or glipizide extended-release formulations are recommended in combination with metformin. These long-acting sulfonylureas are preferred over the commonly prescribed glyburide, given the relatively comparable glycemic-lowering efficacy but decreased risk for build-up of active compound or metabolites causing hypoglycemia in individuals with impaired renal clearance [38]. Moreover, glyburide's association with prolonged hypoglycemia, especially in an elderly patient population, and its apparent ability to stimulate insulin secretion at low plasma glucose concentrations discourage its use over these other agents [39]. Overall, the benefits of the sulfonylurea class are that they provide rapid glucose lowering that becomes of paramount importance in a symptomatic patient as opposed to other noninsulin agents that require slow dosage titrations or several weeks to reach maximal clinical efficacy. Sulfonylureas have a long history of clinical use, and as such are more reassuring from a long-term safety standpoint compared with newer therapies. The real advantage is their relatively lower cost and the availability of generic formulations that may be critical for some patients who may be taking many medication to manage their diabetes. On the downside, this class of agent is associated with a risk of hypoglycemia and weight gain.

The DPP-4 inhibitor class includes sitagliptin and saxagliptin in the USA, with vildagliptin being available in Europe and in some other countries. This class of agents is generally well tolerated and allows simple oral dosing. A1C reductions in the range of 0.6 to 1.0 percentage points can be expected with this class of diabetes oral agents [40,41]. The DPP-4 inhibitors target postprandial hyperglycemia through a combination of modest increase in glucose-dependent insulin secretion and suppression of postmeal glucagon secretion. Interestingly, in a head-to-head comparison trial, the DPP-4 inhibitors appeared to provide similar A1C lowering to sulfonylureas, with the added benefit of weight neutrality and a lower risk of hypoglycemia [42]. It is important for clinicians to note that the magnitude of A1C reduction expected from any glucose-lowering agent is heavily influenced by the starting A1C. In fact, a recent review states that 35% of the glucose-lowering capacity of most agents is dependent on the starting A1C level [43]. Recently, the combination of metformin and sitagliptin has been approved by the US FDA as initial therapy for the treatment of T2D. The combination of these two oral agents resulted in additive A1C lowering compared with the two agents used as monotherapy [44]. Overall, the addition of a DPP-4 inhibitor to metformin does not lead to hypoglycemia while maintaining weight neutrality. These compounds can be used in patients with moderate-to-severe renal impairment at a reduced dosage. The drawback is that this class of medication is of a higher cost to the patient, and being newer agents, they lack the long-term safety data found with agents such as metformin and sulfonylureas. This class of diabetes oral agents will probably expand quickly, with several DPP-4 inhibitors in Phase III clinical studies.

The GLP-1 agonist class includes exenatide and liraglutide with several other GLP-1 agonists currently in clinical development. In addition to fostering A1C reductions, which are slightly greater than those typically seen with a DPP-4 inhibitor [45], the agents yield an approximately 1.0 percentage point reduction in A1C. These agents uniquely hold the potential for contributing to modest weight loss and do not independently cause hypoglycemia [46,47]. In general, the longer-acting GLP-1 agonists, such as liraglutide, and the once-weekly agents in development possess slightly greater A1C reduction capabilities than the shorter-acting GLP-1 agonists, such as regular formulation exenatide, owing to their greater suppression of elevated fasting plasma glucoses. However, this is at the expense of some diminution of the flattening of postprandial glycemic excursions seen with the shorter-acting GLP-1 agonist agents. The majority of patients initiating GLP-1 agonist therapy lose weight. This weight loss has been shown to improve other cardiovascular risk factors including lowering blood pressure, raising high-density lipoprotein and lowering triglycerides along with improvements in cardiac risk biomarkers [48]. Exenatide is routinely dosed

two times per day, normally before breakfast and the evening meal. A six-way crossover study with fixed breakfast demonstrated that injecting exenatide 15–60 min prior to the meal had the most pronounced flattening effect of the postmeal rise in glucose compared with placebo [49]. When the two GLP-1 agonists were compared head-to-head, liraglutide demonstrated slightly better A1C lowering with equivalent weight loss [50]. The GLP-1 agonists are among the most expensive diabetes agents, and must be given by subcutaneous injection once or twice daily. Gastrointestinal side effects such as nausea are relatively common upon initiation or upward dosage titration but tend to be mild and self-limited in the majority of patients, dissipating over time. Being newer agents as well, long-term safety data on their use are lacking but this is being carefully studied.

The final option of the far right of the two-drug therapy row of the IDC algorithm is the addition of TZD to metformin therapy. Pioglitazone is the recommended agent, given the concern over increased cardiovascular events that has been raised regarding rosiglitazone [51,52]. While meta-analyses have raised concerns over increased cardiovascular risks with rosiglitazone, this has not been the case with pioglitazone, which did show a reduction in cardiovascular risk in a secondary analysis of the ProActive randomized clinically controlled trial [53]. The TZD class has been demonstrated to be useful in targeting insulin resistance (e.g., nonalcoholic fatty liver disease), with pioglitazone in particular having a salutary effect on improving the overall lipid profile and thus cardiovascular risk. Pioglitazone is higher in cost than the sulfonylureas or metformin. This class' propensity toward causing fluid retention contributes to its risk of causing or exacerbating peripheral edema, macular edema and congestive heart failure, and the latter is clearly described in a black box warning. Both the fluid retention and the deposition of subcutaneous adipose tissue induced by this class of agents can lead to weight gain. Another risk of this class appears to be the association with duration of use of these agents for more than 2 years leading to an increase risk of bone fractures [54]. This 'off target' effect of TZDs appears to influence the selection of bone marrow progenitor cell lines to differentiate towards adipocytes rather than osteoblasts, eventually resulting in decreased bone formation and bone loss, leading to higher fracture rates [55].

Along the two-drug therapy tier and throughout the algorithm, the subtly increased shading in the central portion of the algorithm is meant to imply the most physiologic (and potentially beneficial) treatment approach with 'all things being equal', such as cost and long-term safety data **(Figure 1)**. In an ideal setting, one would want to avoid weight gain and potentially achieve weight loss to treat one of the major underlying pathologic mechanisms leading to the development of T2D, and to do so without increasing the risk of hypoglycemia. Therapies that may preserve β-cell function, or at least reduce the ongoing β-cell functional loss seen in T2D, may be of added benefit in the long-term treatment of this disorder. Those therapies that reduce the risk of hypoglycemia will likely improve patient adherence over the long treatment course of the disease. Thus, the incretin area is shaded in tier two as there may be concern that sulfonylureas do less to preserve β-cell function over the long haul. The results of A Diabetes Outcome Progression Trial (ADOPT) are potentially enlightening in this regard, as sulfonylurea therapy had the least durability in maintaining targeted glycemic control when compared with metformin and rosiglitazone [56]. The TZD class, while useful in this regard as well, is not as prominent in the IDC algorithm owing to concerns regarding an increased risk of congestive heart failure and weight gain, and a growing concern over the long-term detrimental bone effects, which would seem to outweigh its benefits.

Thus, if cost were not an issue, it would make the most physiologic sense to use metformin and incretin-based therapy along with aggressive efforts at lifestyle modification to achieve maximal glycemic lowering with concomitant weight loss and little risk of hypoglycemia. Use of GLP-1 agonist therapy has been demonstrated to improve β-cell function, as determined by the homeostasis model assessment of β-cell function (HOMA-B) [48]. However, the improvement in β-cell function was not maintained after 1 year of treatment following discontinuation of GLP-1 therapy, returning to pretreatment baseline levels within 4 weeks of discontinuing therapy [57]. Interestingly, preliminary reports at the 2010 ADA annual scientific sessions reported that markers of improved β-cell function (disposition index and first-phase insulin secretion) remained significantly greater at 4 weeks after discontinuation of exenatide therapy in a small group of individuals who had been treated

continuously for 3 years [58]. Nonetheless, improving glycemic control without increasing the risk of hypoglycemia or weight gain would be expected to fare the best in terms of patient adherence, and has been shown to result in improved patient satisfaction in relation to other agents [45]. Given the growing understanding of T2D as a systemic disorder with abnormalities in coagulation, endothelial dysfunction and fatty acid metabolism, this differential effect (GLP-1 agonists causing weight loss compared with other therapies that are weight neutral or cause weight gain) compared with other agents would be expected to translate into improvements in the overall cardiovascular risk profile. In addition, there is growing evidence that GLP-1 receptors on myocardial cells and endothelium as well as other tissues may exert a statutory effect on the cardiovascular system, further improving its function and decreasing cardiovascular risk. If one subscribes to the lipocentric view of diabetes, where excessive caloric intake leads to ectopic deposition of fatty acids in skeletal muscle and the liver, inducing insulin resistance in these tissues and the deposition of fatty acids in β-cells, inducing lipotoxicity with reduced insulin secretion, then therapies that are weight neutral, or result in weight loss, would potentially have added benefit in terms of improving glycemic control and reducing the risk of complications [59].

Three-drug therapy

If glycemic control is not established after 3 months on two-drug therapy, or if the regimen is not sufficient to maintain glycemic control, the next step is to proceed to three-drug therapy. Two schools of thought occur at this point. The first school emphasizes that once a patient fails to achieve adequate glycemic control with two noninsulin agents, the patient is becoming relatively insulinopenic and requires insulin therapy rather than the addition of yet another oral agent or GLP-1 agonist therapy. In such individuals, pushing three- or even four- or five-drug oral and noninsulin therapy is unlikely to achieve therapeutic targets and only delays the successful achievement of adequate glycemic control, thus exposing the individual to increased risks of hyperglycemia and its complications, as well as increased risks of adverse reactions or drug–drug interactions from pushing noneffective drugs to higher dosages [60]. The ADA/EASD consensus algorithm would support this concept even more aggressively by including the addition of background (basal) insulin as one potential second step if metformin and MNT are not sufficient to achieve glycemic targets [7]. The second (less optimal) school of thought emphasizes that the addition of a third noninsulin agent will provide a reasonable chance of allowing the patient to achieve glycemic control while avoiding the 'hassle' of initiating insulin. Both schools are represented in the three-drug therapy section of the algorithm. The IDC algorithm attempts to steer practitioners to insulin therapy at this point but acknowledges that many patients and physicians may at least demand a trial of three-drug noninsulin therapy before acquiescing to the need for insulin administration.

Many of the same considerations used for selecting a two-drug therapy apply to selecting the appropriate three-drug therapy. For example, if the patient is being treated with metformin and sulfonylurea because cost is an overriding concern, the addition of background (basal) insulin may be the next best option. NPH insulin is a cost-effective alternative to long-acting insulin analogs that is able to provide similar A1C lowering at the expense of an increased risk of hypoglycemia [61]. In terms of glycemic control, the addition of either background insulin or a TZD to patients inadequately controlled on a combination of sulfonylurea and metformin resulted in a similar reduction in A1C of approximately 1.4 percentage points, with a greater reduction in fasting glucose with background insulin [62]. Based on the results of the 4T trial, it would appear that the initiation of a basal insulin would work best in a primary-care setting, resulting in improved glycemic control with less weight gain and hypoglycemia compared with other insulin regimens, and is among the conceptually easier insulin initiation programs for both primary-care providers and patients [63]. The addition of basal insulin to patients currently treated with metformin- and incretin-based therapy makes sense physiologically. Metformin reduces hepatic glucose output, incretin therapy stimulates insulin secretion and reduces postmeal hyperglucagonemia and background insulin lowers fasting and between-meal hyperglycemia. In support of this is the recent approval of the DPP-4 inhibitor sitagliptin with insulin by the FDA and a publication by Buse *et al.* demonstrating that twice-daily exenatide added to background insulin alone or in combination with metformin and/or pioglitazone significantly reduced A1C

and weight versus placebo added to background insulin alone or in combination with metformin and/or pioglitazone [64]. Alternatively, if patients are not treated with an incretin-based therapy at this point, the addition of a DPP-4 inhibitor or GLP-1 agonist can be considered if concern over weight gain and hypoglycemia are overriding factors. For example, the addition of GLP-1 agonists to patients inadequately controlled on sulfonylurea and metformin showed a reduction in A1C of approximately 1 percentage point accompanied by modest weight loss [65].

Multidose insulin therapy

If glycemic control is not established after 3 months on three-drug therapy or if the regimen is not sufficient to maintain glycemic control, the next step is to proceed to multidose insulin therapy. If patients present with extreme hyperglycemia, defined as A1C greater than 11%, fasting blood glucose greater than 300 mg/dl and/or random plasma glucose greater than 350 mg/dl, multidose insulin therapy is recommended to overcome glucotoxicity associated with high blood glucose [66,67]. The IDC algorithm lists three multidose insulin therapies for consideration. The first is initiating background and mealtime (main meal) ± noninsulin agents. This regimen is primarily used for transitioning from three-drug therapy when background insulin is part of the regimen coupled with the need to start mealtime insulin gradually before the largest meal, the meal with highest carbohydrate content or the meal that results in the highest postprandial excursion. To obtain this data, ask the patient to test before and 2 h after meals for 1 week to guide decision making. This approach of adding bolus insulin first at the largest meal (highest glucose excursion) then over time, adding a bolus to other meals one at a time, is often referred to as basal plus therapeutic approach to advancing from basal to basal bolus insulin [68]. The IDC algorithm names insulin regimens using patient-friendly terms such as background and mealtime insulin instead of the traditional patient-confusing terms 'basal' and 'bolus' insulin, respectively. A second and more common option is to initiate multidose insulin therapy using premixed insulin that provides both background and mealtime coverage. Premixed insulin regimens have been shown to dramatically improve glycemic control when added to combination oral agent therapy [69]. Patients strongly preferring the increased convenience of fewer injections per day versus more traditional intensive insulin regimens (background and mealtime or basal/bolus) and in whom meal timing and content are relatively stable and consistent may find this regimen quite useful. This approach of using only one type of insulin requires only one copayment for medications and there is less opportunity for some patients to mix up two different insulins. Patients with a more variable or erratic meal pattern following the premixed insulin regimen may experience increased risk of hypoglycemia if meals are delayed. Another limitation of the premixed insulin regimen is related to the fixed dosage ratio for short- and intermediate-acting insulin. For example, in some patients who may require a higher dose of intermediate-acting insulin to control afternoon or pre-evening meal glucose, the morning dose of the premix insulin cannot be increased further due to the shorter-acting insulin component, resulting in premeal hypoglycemia at the midday meal or the occurrence of afternoon hypoglycemia at the higher dose.

Note that the arrows under multidose insulin therapy point to background and mealtime (all meals) traditional intensive insulin therapy (or multiple daily injection) **(Figure 1)**, providing the most flexibility in terms of dosage adjustment and the timing of injections in response to varying meal and snack content and timing. This regimen provides the patient with the best chance for achieving tight glycemic control because it is a more physiological approach to insulin delivery with the ability to adjust insulin using more sophisticated techniques such as the insulin:carbohydrate ratios. A recent study showed that individuals with T2D could advance to basal bolus (background and mealtime) insulin therapy and achieve A1C levels close to 6.5% with minimal hypoglycemia with or without the use of carbohydrate counting to direct the dosing of the bolus insulin [70].

Conclusion & future perspective

The IDC Treatment of T2D Algorithm seeks to provide the primary-care provider with a practical, evidence-based, easy to use guideline to initiate and advance therapy for T2D. It contains recommendations based on the patient's metabolic state as well as clinical factors such as hypoglycemia risk, the impact of therapy on weight and the potential for adverse events. It also takes into account patient factors such as cost and medication delivery and dosing. The earlier one initiates effective glycemic control,

the easier it appears to be to maintain control, limit excessive life-time glucose exposure and reduce morbidity and mortality [71].

All clinicians treating T2D today know that effective management requires an aggressive multifactorial approach to risk factor management [72,73]. While this article has focused on a road-map or algorithm for improving glycemic control, it is critical to treat and target blood pressure and lipids as well. The IDC has made its glucose, blood pressure and lipid management algorithms for T2D available on its website [103]. In addition, an emphasis on not using tobacco and the use of low-dose aspirin in appropriate patients with cardiovascular disease, or at very high risk for cardiovascular disease, can help minimize the long-term complications of diabetes [10].

Finally, a series of algorithms that help guide care, and generate a dialog among care providers and between providers and patients is only one component of an effective diabetes care system. Working collaboratively as part of a patient-centered care team in a care system dedicated to quality improvement and maximizing the input and experience of the patient have been additional components we have found to be critical to successful diabetes management.

Metformin is secure in its place as the first-line pharmacologic therapy for most individuals with T2D, given the following:

- Its established long-term clinical use without any new safety signal and a very low risk of lactic acidosis;
- Its efficacy being among the best in terms of glycemic lowering;
- Its widespread availability and low cost;
- Its potential added metabolic benefits in terms of cardiovascular risk and cancer;
- Its lack of propensity to cause weight gain or hypoglycemia.

The choice of second-line agents or monotherapy in those individuals who cannot use metformin must be individualized based on several factors carefully weighed up by both the patient and treating clinician, including underlying pathophysiologic mechanisms, cost, efficacy, potential for weight gain and hypoglycemia, route of administration and dosing frequency.

Here, the advent of incretin-based therapies has expanded the treatment options for patients, providing them with the opportunity to improve glycemic control with a minimum risk of hypoglycemia while avoiding weight gain, either with weight neutrality in the case of DPP-4 inhibitors or with the unique potential for simultaneous weight reduction in the case of GLP-1 receptor agonists. Cost remains the major barrier for this class of agent, particularly with the GLP-1 receptor agonists, for which being injectable therapies may also present a barrier to some patients.

While some patients and physicians may prefer proceeding to the addition of a third oral agent if two-drug therapy is unable to achieve glycemic targets, the majority of experts would recommend proceeding to insulin therapy at that point. The 4T trial suggests that the addition of a basal insulin at this point may be preferred over more complex regimens, and would have the added benefits of improving glycemic control while mitigating the degree of weight gain and risks of hypoglycemia seen with multidose insulin regimens.

With the increased appreciation of the risks of therapies that improve glucose control at a cost of increased risk of hypoglycemia and weight gain, potentially exacerbating the other metabolic parameters, the sequential use of metformin, GLP-1 receptor agonists and a basal insulin may have theoretical advantages that, it is hoped, may translate into long-term clinical benefits. Trials to evaluate the comparative effectiveness of these different approaches are sorely needed. The T2D treatment algorithm will become more complex in the future with the development of new classes of oral agents, GLP-1 agonists and insulin.

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