Guideline Approach to Therapy in Patients With Newly Diagnosed Type 2 Diabetes

ITAMAR RAZ, MD

Both the prevalence and incidence of type 2 diabetes are increasing worldwide in conjunction with increased Westernization of the population's lifestyle. Type 2 diabetes is still a leading cause of cardiovascular disease (CVD), amputation, renal failure, and blindness. The risk for microvascular complications is related to overall glycemic burden over time as measured by A1C (1,2). The UK Prospective Diabetes Study (UKPDS) 10-year follow-up demonstrated a possible effect on CVD as well (3).

A meta-analysis of cardiovascular outcome in patients with long disease duration including Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) suggested that in these populations the reduction of ~1% in A1C is associated with a 15% relative reduction in nonfatal myocardial infarction (4).

Most antihyperglycemic drugs besides insulin reduce A1C values to similar levels (5) but differ in their safety elements and pathophysiological effect. Thus, there is a need for recommending a drug therapy preference.

While the positive effects on prevention of microvascular complications were demonstrated with the various antihyperglycemic drugs (1,2,6,7), several questions are left open regarding this therapy in newly diagnosed type 2 diabetes:

1. What is the comparative effectiveness of antihyperglycemic drugs on other long-term outcomes, i.e., β-cell function and cardiovascular morbidity and mortality?
2. What is the comparative safety of these treatments, and do they differ across subgroups of adults with type 2 diabetes?
3. Should we combine antihyperglycemic drugs at the time of diagnosis according to their pathophysiological effect to address the different pathologies leading to hyperglycemia?

Most leading guidelines suggest adding one of several antihyperglycemic drugs (5,8,9) when lifestyle and metformin fail to keep A1C at target unrelated to these questions. The previous American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus statement suggested a preferable order of drugs (5), while the AACE/ACE Diabetes Algorithm for Glycemic Control suggested starting treatment with combination therapy in naïve patients with A1C >7.6% (10). The Canadian Clinical Practice Guidelines suggested adding one of several second drugs after metformin in patients with A1C >7% (8). Similarly, the recently published ADA/EASD position statement suggested leaving the decision of which drug to add to the treating physician (9). The above-mentioned guidelines are mainly based on drug efficacy and safety and do not necessarily address the various pathophysiology defects leading to hyperglycemia and increased risk for CVD in these patients. The case for initiating combination therapy that addresses the different pathophysiological faults in newly diagnosed type 2 diabetic patients in order to preserve near-normal glycemic durability is presented in this issue by DeFronzo, Eldor, and Abdul-Ghani (11). I will present the case for guidelines while referring and critiquing the approach of DeFronzo, Eldor, and Abdul-Ghani and suggest another option for a middle-of-the-road treatment method.

Case for guidelines

Evidence-based recommendations should be at the core of the guidelines. Not all practice guidelines on antihyperglycemic drugs, however, are consistent with available evidence (12). Patient enrollment in clinical studies is also based mainly on baseline A1C, and treatment of a comparator is sometimes chosen unrelated to its pathophysiologic effect on hyperglycemia.

Our past experience with antihyperglycemic drugs is that recommendations to stepwise increase these drugs whenever A1C is above target might fail to prevent disease progression (1,6), necessitating intensive insulin therapy over time. This might be due to delayed reaction by the physician to a patient's change in A1C (13). One possible reason for this delay is that the other antihyperglycemic drugs (other than metformin), i.e., sulfonylureas and peroxisome proliferator–activated receptor (PPAR)-γ, have side effects that discourage physicians from recommending them as soon as A1C is above target (13–21). Introduction of insulin therapy in patients not at target, in particular, is also delayed substantially (22). At this stage, aiming to target with intensive insulin therapy might increase the risk for morbidity and mortality while the already long hyperglycemic exposure still puts the patient at great risk for late micro- and macrovascular complications (6,23–25). The newer

From the Diabetes Unit, Hadassah University Hospital, Jerusalem, Israel.
Corresponding author: Itamar Raz, ntv502@netvision.net.il.
This publication is based on the presentations from the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Ethicon Endo-Surgery, Janssen, Medtronic, Novo Nordisk, Sanofi, and Takeda.
DOI: 10.2337/dcS13-2035

See accompanying article, p. S127.

available drugs (incretins as well as sodium glucose cotransporter 2 inhibitors), owing to their efficacy and relatively mild side effects, could change physicians' inertia in such a way that they will prescribe these drugs at a much earlier stage—as soon as A1C is above target. This earlier intervention could prevent treat to failure and be as effective as early combination therapy.

Although treatment focused on simultaneously reversing the various pathophysiological abnormalities would be a logical therapeutic approach, we still do not have evidence of its superiority over current guideline treatment on durability of β-cell function and reduction of micro- and macrovascular complications. Moreover, combination therapy or triple therapy suggested by DeFronzo, Eldor, and Abdul-Ghani (11) carries some short- and long-term safety concerns and high cost over time that prevent them from becoming the standard of care at the early stage of diabetes (14–19,26–34).

Lifestyle change to correct the pathophysiological abnormalities of insulin resistance and β-cell dysfunction should precede and be part of drug therapy (35,36). Keeping the proper lifestyle, however, is challenging and not achievable to satisfactory levels in most of our patients (36). Moreover, lifestyle by itself does not always lead to patients' ability to achieve target A1C, and for this reason most leading guidelines recommend that newly diagnosed type 2 diabetic patients not at target combine proper lifestyle with metformin. Other than insulin, the treatment options include the following drug classes, which should preferably be started as monotherapy or combination therapy with metformin.

Specific advantages and disadvantages of individual main drug classes

Metformin. Metformin as first-line therapy is in the general consensus, since its efficacy is similar to other antihyperglycemic drugs—besides insulin. It has a large safety margin and can be used by most patients other than a small number who experience gastrointestinal side effects. It decreases hepatic glucose production, has a mild effect on peripheral resistance, and increases both total and active endogenous glucagon-like peptide (GLP)-1 in response to food (37). Metformin might also be cardioprotective, mainly in obese type 2 diabetic patients (38). Moreover, recently published observational studies, as well as animal and cell-line studies, suggest that this drug might be effective in reducing cancer-related morbidity (39,40). Thus, metformin is accepted as first-line therapy by both guidelines and pathophysiologic reasoning.

Sulfonylureas and meglitinides. There are two classes of oral antihyperglycemic drugs that stimulate release of insulin from β-cells: the sulfonylureas and meglitinides. Sulfonylureas are one of the most widely used drugs for treatment of type 2 diabetic patients. They increase responsiveness of β-cells to glucose and to non-glucose secretagogues, resulting in more insulin being released at all blood glucose concentrations. They are effective as long as patients have residual β-cell function. These drugs may also have extrapancreatic effects, such as to increase tissue sensitivity to insulin, although the clinical importance of these effects is minimal. Sulfonylureas usually lower A1C by 1–2% (20).

Sulfonylureas are usually well tolerated, with hypoglycemia and weight gain being the most common side effects. Their long-term durability effect is inferior to metformin and PPAR-γ (21). Some studies suggest that sulfonylureas may be associated with increased cardiovascular morbidity and mortality (41). This is not supported, however, by results from the UKPDS, which reported no increase in fatality for patients taking sulfonylurea treatment (1).

Due to their side effects and limited effect on long-term blood glucose control (21), there is a tendency to replace sulfonylureas with drugs that better preserve β-cell function and do not have similar side effects. Today, the decision to use sulfonylureas is strongly related to their very low cost.

The meglitinides, repaglinide, and nateglinide are short-acting glucose-lowering drugs for treatment of patients with type 2 diabetes alone or in combination with metformin. They are structurally different from sulfonylureas and work via different receptors but act similarly by regulating ATP-dependent potassium channels in the β-cells, thereby increasing insulin secretion (42). Hypoglycemia and weight gain are the most common adverse effects of these drugs.

PPAR-γ: pioglitazone. The most effective drug that was shown to maintain long-term durability of blood glucose control (up to 4 years) by reducing insulin resistance and improving β-cell function comes from the PPAR-γ family (21). These drugs reverse the typical type 2 diabetes lipid deposition abnormalities by reducing the level of fat deposited in muscle, liver, and pancreas, improving both insulin sensitivity in the muscle and liver and β-cell function. Their blood glucose-lowering efficacy is similar to that of other antihyperglycemic drugs besides insulin (43,44)

PPAR-γ therapy over time has some safety concerns. Body fat gain is a major drawback of treatment with glitazones. Some evidence suggests that the fat is redistributed in favorable direction from visceral to subcutaneous depots, but no long-term follow-up is yet available to support it. Although this kind of weight gain decreases insulin resistance, it is still a burden for older and obese type 2 diabetic patients with exercise limitations and arthropathy. Fluid accumulation related to these drugs is also a significant issue; 10% of the patients receiving glitazones will experience peripheral edema, and this number increases considerably when glitazones are given in combination with insulin and dihydropyridine calcium channel blockers for the treatment of hypertension. In patients with CVD or at high risk for CVD, as well as patients with renal dysfunction, PPAR-γ may alter the already precarious volume status leading to progression of ischemia or heart failure (14). Other obstacles for treatment include an increase in bone fractures (mainly in postmenopausal women [15]), macular edema (16), and, recently reported, suspicion of increased risk for bladder cancer (17–19).

Incretins. The endogenous incretins, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, are peptide hormones secreted from endocrine cells in the small intestine. Both of these molecules activate insulin secretion in healthy individuals; GLP-1 also inhibits glucagon secretion and slows gastric emptying.

GLP-1 and GIP delay gastric emptying and reduce food intake, which explains the positive effect of incretin mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors on weight. The incretins have also been shown to have a sustained improvement in glycemic control over 3 years (45). A wide range of cardiovascular benefits have also been claimed, such as lowering of blood pressure and postprandial lipids (46).

In physiological circumstances, GLP-1 and GIP have an extremely short half-life, as they are almost immediately inactivated by the DPP-4 enzyme (47). GLP-1 homologs (exenatide and lixisenatide) or

analogs (liraglutide, dulaglutide, and albiglutide) are injectable peptides resistant to the degradation by DPP-4 enzymes. These products are administered once or twice daily or once weekly. After injection of these products, GLP-1 levels are increased to much higher levels than those observed with DPP-4 inhibitors, and the levels stay high even in fasting circumstances. Moreover, these high levels are also present in the peripheral circulation (48). The elevation of circulating incretin concentrations is a desired effect in patients with type 2 diabetes, as it restores the incretin effect on β-cells that has been shown to be reduced in type 2 diabetes (48).

The GLP-1 receptor agonists are generally well tolerated, although administration of exenatide is dose-dependently associated with nausea. Liraglutide is also associated with nausea, a side effect that is less dose dependent and declines in frequency within 4 weeks of treatment in most patients (49).

GLP-1 seems to have wider effects on the function and survival of cells that express its receptor. In vitro, insulin-gene transcription is stimulated while cell apoptosis is inhibited by GLP-1 receptor activation that even stimulates cell growth, which raises the issue of whether activation of the GLP-1 receptor pathway might have positive or negative effects when chronically used for the treatment of type 2 diabetes (26).

There have been reports suggesting that both treatments with exenatide (27) and liraglutide (28), the most common GLP-1 receptor agonists, are associated with an increased risk of pancreatitis. As chronic pancreatitis is also a known risk factor for pancreatic cancer through cytotoxicity of inflammatory cytokines, reactive oxygen species, and proliferation (29), there might be an increased risk of pancreatic cancer as well.

Evaluation of the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) in 2011 by Elashoff et al. (30) showed a 6- to 10-fold increase in pancreatitis in patients treated with the DPP-4 inhibitor sitagliptin or with exenatide in comparison with patients treated with the control drugs rosiglitazone, nateglinide, reparglinide, or glipizide (43 events). The reported event rate for pancreatic cancer was 2.9 times higher for exenatide (81 events) and 2.7 times greater for sitagliptin (16 events) compared with control therapies (13 events). The absolute numbers of these events are of course very small compared with the vast number of patients included in the database between 2004 and 2009. It is possible that chronic pancreatitis and premalignant lesions could be subject to GLP-1 stimulation and progression to malignancy. This publication was subsequently criticized for inappropriate use of FDA AERS, which the FDA itself does not recommend for epidemiologic analysis (50).

Moreover, a retrospective cohort study of a large medical and pharmacy claims database performed on >786,000 patients did not find an association between the use of exenatide or sitagliptin and acute pancreatitis (51). An additional consideration in evaluation of the risks for cancer from these drugs is the possibility of confounders, such as the link between high BMI and cancers, which is likely to be a confounder for a drug specifically given to more obese people (52).

It has also been observed in preclinical studies that incidence of thyroid C-cell tumors was increased in rodents treated with GLP-1 analogs (31). Therefore, monitoring for thyroid cancer has been a focus in the clinical development plan of all DPP-4 inhibitors and GLP-1 receptor agonists, but thus far the data have been reassuring.

Nonetheless, the preclinical finding that the incidence of an extremely rare cancer is increased should be a cause for concern. In the AERS database, incidence rate of thyroid cancer in patients treated with exenatide was clearly higher, with an odds ratio of 4.7 (30 events) compared with sitagliptin (2 events) and the panel of control drugs (3 events) (30).

The safety of constant DPP-4 or GLP-1 therapy over time is not yet clear. Presently, the benefits of using DPP-4 inhibitors or GLP-1 receptor agonists for treatment of type 2 diabetes outweigh the risks. Nonetheless, their safety profile should be monitored and their indications should be widened cautiously. The issue of pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis as well as the increased risk for cancer (32,33,53,54), has not yet been resolved. In addition, the issue of cardiovascular safety (these drugs sometimes cause tachycardia), as well as other unknown safety issues related to these new drugs is still under investigation (34).

Other antihyperglycemic drug options

Other antihyperglycemic drugs including α-glucosidase inhibitors, pramlintide, colesevelam, and quick-release bromocriptin are in general less effective, associated with adverse events that limit their use as second or third line in patients who fail to reach target with metformin, or there is very limited experience of their use; they will not be discussed further.

Identifiable clinical groups of patients

Both A1C target and antihyperglycemic drugs used to achieve the target might need specific considerations for identifiable clinical groups of patients, i.e., patients with comorbidities or patients with short life expectancy. In this counterpoint article, however, we focus on patients with long-term good prognosis.

Economic considerations

There is a paucity of studies today to demonstrate the cost-effectiveness of relatively new antihyperglycemic drugs in diabetes. While lifestyle intervention has relatively well-established evidence from an economic viewpoint, there are few studies relating to the cost-effectiveness for pharmacological treatment in diabetes prevention and treatment except metformin. Metformin is currently the only drug with proven cost economics, although it is less cost-effective than lifestyle intervention when used in people with prediabetes (55). In the Diabetes Prevention Program (DPP), metformin intervention was cost-effective in younger participants but not in subjects older than 65 years of age (35). Certainly, further studies relating to cost-effectiveness of other drugs with proven treatment-effectiveness are needed.

A major decision regarding treatment relates to cost-effectiveness. In most of the world, mainly, large parts of Asia, Africa, Latin America, and Central and Eastern Europe, the accessibility of patients to relatively new drugs is limited because of their high costs. Furthermore, even in countries with better economic situations, medical insurance agents demand evidence for long-term efficacy and safety. This is in view of the large investments necessary in order to introduce new drugs. It is hard to imagine insurance companies approving combination therapy, including pioglitazone and GLP-1 agonists, at high cost without being certain that the patient will benefit from these drugs whether with regard to durability or prevention of late complications. Pioglitazone has recently become generically available, which has significantly reduced its cost.

Stepwise treatment according to guidelines: is it justified?

The answer is yes, since under current guideline therapy, with the availability of newer drug classes with minor side effects, using a stepwise increase in antihyperglycemic drug therapy as soon as A1C is above target can be implemented and might prevent disease progression similarly to combination or triple therapy. Moreover, a large proportion of patients will maintain near-normal A1C levels for many years under proper lifestyle and monotherapy, i.e., metformin (2), sulfonylurea, or early insulin therapy (1). We cannot, however, identify these patients in advance. Using combination or triple therapy from the beginning in these patients in an effort to correct the different pathophysiological defects seems unjustified, since it might hinder efforts to identify the drug to which these patients respond or do not respond and might complicate the diagnosis of relation of side effects to the drug.

On the other hand, an initial early stepwise increase from monotherapy to combination therapy when A1C is above target may maintain durability similar to that which can be achieved by starting with combination therapy or triple therapy as suggested by DeFronzo (11). Stepwise addition, however, allows evaluation of drug efficacy and possible side effects. Moreover, at the very early stage of diabetes or prediabetes, responses of patients with near-normal A1C to treatment, even if effective, are often marginal. Using combination or triple therapy at this stage may result in treating a patient for years with ineffective or unnecessary drugs with their concomitant side effects and safety issues at high cost.

The current approach of choosing drugs in relation to their efficacy and safety and addressing part of the pathophysiological faults still seems justified. The recent ADA/EASD position paper recommends the addition of one of five antihyperglycemic drugs beyond metformin when A1C is above target in a stepwise manner—acknowledging their side effects and safety (9).

On the other hand, in order to prevent β-cell loss and late complications the time for aggressive treatment should be at the very early stages of the disease, aiming at A1C levels of <7% and, if possible, at a prediabetic state of levels ≤6–6.5% (1,2,6,23). If both lifestyle changes and metformin do not normalize blood glucose levels, targeting reduction of insulin and incretin resistance and improvement in β-cell function is justified. Patients would then need early and more aggressive therapy. The dilemma of such an aggressive approach started at the early stage of diabetes lies in lack of evidence for long-term efficacy and safety using these drugs, while their short-term side effects are sometimes still bothersome and their cost over time might not be justified.

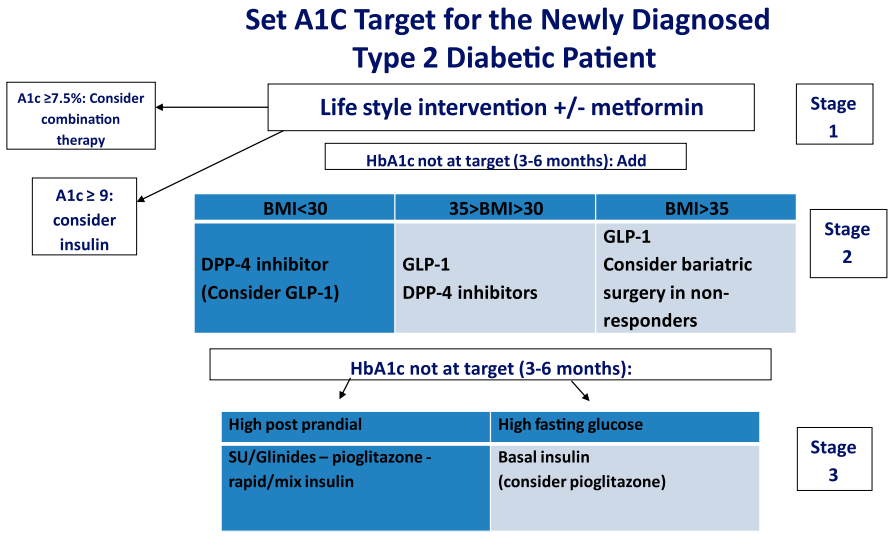

Figure 1—*Guideline approach to drug therapy in newly diagnosed type 2 diabetic patients not at target. First, set your target A1C (8). If not at target, stage 1: Start with lifestyle and metformin. If A1C ≥7.5% (10) or ≥9% (9,10), consider short-term combination therapy or insulin, respectively. Stage 2: If A1C is not at target after 3–6 months of metformin therapy, suggest adding incretin therapy (in relation to BMI). For patients resistant to GLP-1 therapy with BMI >35 kg/m^2 who do not reach target, consider bariatric surgery or proceed to stage 3. Stage 3: If not yet at target, recommend adding a basal insulin analog—mainly in patients with high fasting or preprandial glucose—and pioglitazone, sulfonylurea (SU)/glinides, or rapid/premix insulin in cases of postprandial hyperglycemia.*

It seems that in order to prevent treatment to failure in newly diagnosed diabetic patients on the one hand and to ensure high levels of safety and justify the cost on the other hand, we should take a midway approach. We support the ADA/EASD position paper guidelines based on drug efficacy and safety. However, in order to prevent β-cell loss and dysfunction and long-term exposure to hyperglycemia, we suggest intervention at an earlier stage of the disease. This can be accomplished via early aggressive therapy beyond metformin with one drug when A1C is >6.5%, if possible with a drug that prevents acceleration of β-cell loss and dysfunction on the one hand and does not cause weight gain or hypoglycemia and has a large safety margin and justified cost on the other hand. The midway stepwise approach in treatment of newly diagnosed type 2 diabetic patients following the guidelines described here is presented in Fig. 1. Given the drug efficacy, safety, and cost, incretin therapy (both DPP-4 inhibitors or GLP-1 agonists) might be considered as first-line therapy after metformin, and insulin therapy (mainly long-acting analogs) could be added if A1C is not at target, mainly when fasting or preprandial glucose levels are high. In cases where both fasting and postprandial glucose levels are high, combination of long-acting insulin analogs and GLP-1 agonists should be considered. This treatment approach, based on efficacy as well as side effects and safety of antihyperglycemic drugs, proposes that PPAR-γ, sulfonylureas, and intensive insulin therapy could be the third choice when incretin therapies and basal insulin fail or when economic limitations exist.

Acknowledgments—I.R. is a member of the advisory boards of Novo Nordisk, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Eli Lilly; is a consultant for AstraZeneca, Bristol-Myers Squibb, Johnson & Johnson, and Eli Lilly and Andromeda, HealOr, Insuline, TransPharma, and Teva (Israeli firms); and sits on the speakers bureaus of Eli Lilly, Novo Nordisk, AstraZeneca, Roche, and Johnson & Johnson. No other potential conflicts of interest relevant to this article were reported.

I.R. wrote, reviewed, and edited the manuscript. I.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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