Defining and Achieving Treatment Success in Patients With Type 2 Diabetes Mellitus

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Traditionally, successful treatment of patients with type 2 diabetes mellitus (DM) has been defined strictly by achievement of targeted glycemic control, primarily using a stepped-care approach that begins with changes in lifestyle combined with oral therapy that is slowly intensified as disease progression advances and β -cell function declines. However, stepped care is often adjusted without regard to the mechanism of hyperglycemia or without long-term objectives. A more comprehensive definition of treatment success in patients with type 2 DM should include slowing or stopping disease progression and optimizing the reduction of all risk factors associated with microvascular and macrovascular disease complications. To achieve these broader goals, it is important to diagnose diabetes earlier in the disease course and to consider use of more aggressive combination therapy much earlier with agents that have the potential to slow or halt the progressive β -cell dysfunction and loss characteristic of type 2 DM. A new paradigm for managing patients with type 2 DM should address the concomitant risk factors and morbidities of obesity, hypertension, and dyslipidemia with equal or occasionally even greater aggressiveness than for hyperglycemia. The use of antidiabetes agents that may favorably address cardiovascular risk factors should be considered more strongly in treatment algorithms, although no pharmacological therapy is likely to be ultimately successful without concomitant synergistic lifestyle changes. Newer incretin-based therapies, such as glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors, which appear to have a favorable cardiovascular safety profile as well as the mechanistic possibility for a favorable cardiovascular risk impact, are suitable for earlier inclusion as part of combination regimens aimed at achieving comprehensive treatment success in patients with type 2 DM.

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ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACT NOW = ACTos NOW for the Prevention of Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release and Controlled Evaluation; BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; DREAM = Diabetes REduction Assessment with ramipril and rosiglitazone Medication; GLP-1 = glucagon-like peptide 1; HbA_{1c} = hemoglobin A_{1c}; IGT = impaired glucose tolerance; KORA = Cooperative Health Research in the Region of Augsburg; MI = myocardial infarction; MONICA = MONitoring of trends and determinants in CARDiovascular disease; NHANES = National Health and Nutrition Examination Survey; PIPOD = Pioglitazone In Prevention Of Diabetes; PROactive 10 = PROspective pioglitAzone Clinical Trial in macro Vascular Events; TRIPOD = TRoglitazone In Prevention Of Diabetes; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Administration Diabetes Trial

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The United States and the rest of the world are experiencing a rapid increase in the number of patients who have diabetes mellitus (DM) and, with that, the likelihood of a parallel increase in cardiovascular disease (CVD).¹ The most recent information from the National Health and Nutrition Examination Survey (NHANES), conducted between 2003 and 2006, indicated that approximately 8% of the US population had DM² and that more than an estimated 48 million Americans will have DM by 2050.³

Numerous studies have shown that DM-associated morbidity can be reduced substantially by tight glycemic control, which is typically defined as a hemoglobin A_{1c} (HbA_{1c}) level less than 7%. The United Kingdom Prospective Diabetes Study (UKPDS) 33 showed that intensive therapy reduced the risk of developing microvascular complications by 25% compared with conventional therapy ($P < .0099$).⁴ In addition, UKPDS 35 demonstrated that the incidence of clinical complications in patients with type 2 DM was significantly associated with hyperglycemia. For each 1% reduction in mean HbA_{1c} level, there was a 21% reduction in any DM-related end point ($P < .0001$), a 21% reduction in DM-related deaths ($P < .0001$), and a 14% reduction in the risk of myocardial infarction (MI) ($P < .0001$).⁵ Results from NHANES have indicated that glycemic control is improving among US patients with DM. NHANES 1999-2000 reported that only 37% of adults with diagnosed DM achieved an HbA_{1c} level less than 7%⁶; however, that value increased to 49% in NHANES 2001-2002⁷ and increased further to 57% in NHANES 2003-2006.² Although the increased number of patients at goal is noteworthy, it still is insufficient and may reflect the difficulty in sustaining glycemic control in this population over time.² Because of the rapid expansion of the number of patients with DM, it is clear that current treatment paradigms need to be adjusted in their intensity or initiated earlier in the disease course so that larger numbers of patients with type 2 DM will be able to sustain glycemic control in the long term.

Although DM alone is an independent risk factor for CVD, most patients with DM have additional risk factors for macrovascular complications (ie, coronary heart disease, MI, stroke, and peripheral artery disease). For example, hypertension is prevalent in approximately 75% of patients with type 2 DM,⁸ and dyslipidemia and overweight/obesity are common as well, occurring in approximately 70% and 80% to 90% of patients with type 2 DM,

respectively.^{9,10} One study noted that 66% of adults with DM (39,697/59,900 patients) have concomitant hypertension and dyslipidemia.¹¹

Because cardiovascular risk in diabetic patients is multifactorial, successful glycemic treatment, as well as controlling blood pressure (BP) and achieving aggressive lipid goals, can reduce microvascular complications and cardiovascular and cerebrovascular risk in patients and has a greater outcome benefit than improving only glycemic control.^{4,12-14}

Unfortunately, the percentage of patients with DM reaching treatment goals for all 3 parameters of blood glucose, BP, and lipids is much lower than that for achieving glycemic control alone. The percentage of patients with DM who simultaneously achieved goals for HbA_{1c}, BP, and lipids increased from approximately 7% in NHANES 1999-2000 to only 12% in the latest NHANES dataset (1999-2006).^{2,6} Because of the difficulty in achieving multiple metabolic controls in a given patient and across a patient population, the current article redefines treatment success in patients with type 2 DM by prioritizing goals and strategies and by reviewing innovative approaches to patient management in the primary care setting.

DEFINING TREATMENT SUCCESS IN TYPE 2 DM

METABOLIC DEFINITIONS

Traditionally, glycemic control has been used to define the successful treatment of patients with type 2 DM. Guidelines have been established for glycemic control with an HbA_{1c} target goal less than 7.0% according to the American Diabetes Association and 6.5% or less according to the American Association of Clinical Endocrinologists/American College of Endocrinology.¹⁵⁻¹⁷ This metabolic definition follows from the close relationships that have been shown between hyperglycemia and adverse long-term microvascular and macrovascular outcomes in patients with DM.¹⁸

Achieving glycemic control is a critical metabolic goal because hyperglycemia contributes to the progression of DM by adversely affecting both β -cell function and insulin sensitivity.¹⁹ Results from animal studies have shown that chronic hyperglycemia in the presence of decreased β -cell mass markedly decreases the ability of the remaining β cells to respond to an additional glucose stimulus.¹⁹ This impaired insulin response, or glucotoxicity, is reversed by correction of the chronic hyperglycemia and may help explain the abrupt deterioration in glycemic control often seen in relatively stable patients with hyperglycemia. Animal studies have also demonstrated that chronic hyperglycemia results in decreased muscular sensitivity to insulin.¹⁹

Overweight/obesity, which is common in patients with type 2 DM,²⁰ may also contribute to β -cell dysfunction and thus disease progression. Increased tissue levels of free fatty acids associated with overweight/obesity may initially result in β -cell hyperplasia, excess insulin secretion, and below-normal fasting blood glucose levels. If this state is maintained, there is an accumulation of long-chain free fatty acids in β cells and a loss of glucose-stimulated insulin secretion, or lipotoxicity.²¹ Additionally, lipotoxicity is associated with a decrease in β -cell mass through accelerated apoptosis.²²

Glucotoxicity and lipotoxicity are believed to play central and synergistic roles in disease progression in patients with type 2 DM. The glucose- and free fatty acid-induced insulin resistance leads to insulin production insufficient to prevent hyperglycemia and its resultant complications, leading to the failure of this vulnerable β -cell mass.²³ These disease processes are also ongoing in the prediabetes state long before DM is diagnosed.^{24,25} In early disease, aggressive lowering of blood glucose levels with insulin has been shown to enhance β -cell function with some durability of effect, suggesting the importance of glucotoxicity. However, glucotoxicity may not be central to β -cell function in all patients with type 2 DM as the disease progresses and β -cell mass or functionality declines further. Studies with traditional therapies, such as sulfonylureas or metformin, show an effective amelioration of glycemia that may be greater than that seen with newer agents; however, the older agents appear to show a more rapid loss of glycemic control and lesser durability of action, suggesting that other mechanisms may be predominant later in the disease. Furthermore, if glucotoxicity is central to DM development and progression, therapeutic targets, especially earlier in the disease, need to be adjusted to be less than an HbA_{1c} level of 7% if indeed this mechanism is to be effectively addressed.^{24,25}

MECHANISTIC DEFINITIONS

Preservation of β -cell mass and function, although difficult to measure quantitatively, is another indicator of treatment success in patients with type 2 DM. β -Cell mass is constantly renewed through a balance between expansion (eg, neogenesis, replication, and hypertrophy) and involution (eg, apoptosis, necrosis, and atrophy) (Figure 1).²⁶ The state of β -cell function or mass is generally assessed indirectly by measuring insulin response to a glucose challenge.²⁷ However, recently developed nuclear imaging-based probes may help to facilitate in vivo assessments of β -cell mass in human patients, although the practicality is limited.²⁶ Currently, the durability of glycemic control in response to a given agent is our best surrogate parameter of sustained β -cell impact.

FIGURE 1. β -Cell mass plasticity in type 2 diabetes mellitus. β -Cell mass is constantly renewed through a balance between mechanisms of expansion and involution. Reprinted from *Diabetes Obes Metab*,²⁶ with permission from Wiley Blackwell Publishing.

Ultimately, incorporating antidiabetes agents that preserve β -cell function either directly or through decreased β -cell work early in disease management is important because β -cell dysfunction is a key contributor to both the development and the progression of type 2 DM.^{28,29} Treatments that may result in short-term enhancement of β -cell output, such as sulfonylureas, should be used more judiciously than previously recommended because, as monotherapy, they may ultimately contribute to a more rapid β -cell dysfunction and apoptosis; however, whether this is a direct effect of the agent or reflective of increased β -cell work in the setting of ineffective reduction in insulin sensitivity is unclear.²⁹ Metformin, which is currently recommended as initial pharmacotherapy for patients with type 2 DM,^{17,30} is an effective agent to address hepatic insulin resistance and gluconeogenesis, and it modestly helps peripheral insulin resistance in muscle.³⁰ However, because of its moderate effects on peripheral insulin resistance, metformin has not been shown to preserve β cells or enhance their functioning over time.^{26,29} The frequently used combination of metformin and sulfonylureas is both cost-effective and successful in controlling glycemia over time, but this combination is associated with a progressive loss of glycemic control and β -cell function.^{26,29}

Because of their cost-effectiveness and rapid glycemic response, sulfonylureas are also used to manage hyperglycemia in many patients with early type 2 DM. These drugs enhance insulin secretion; however, long-term sulfonylurea treatment is associated with a progressive loss of β -cell function and apoptosis, and this adverse effect is not reduced when the sulfonylureas are combined with metformin therapy.^{26,29}

The thiazolidinediones may conserve β -cell function.²⁶ Studies with the thiazolidinediones have shown that these agents can prevent or delay onset of DM through improved

β -cell function. One plausible mechanism put forth is the “off-loading” of the β cell due to increased insulin sensitivity in peripheral tissues. This insulin sensitization reduces β -cell workload and improves insulin secretory capacity and β -cell function.³¹ Thiazolidinediones also directly affect lipotoxicity at the β cell and appear to have direct effects on β -cell function and mass through this mechanism. Restoration of first-phase insulin secretion, decreased proinsulin levels, and a return to a more normal oscillatory insulin secretory pattern with thiazolidinedione therapy suggest a direct effect on the β cell beyond the reduction of β -cell work.

MANAGING MULTIPLE RISK FACTORS

Patients with type 2 DM are likely to have multiple cardiovascular risk factors.²⁰ Integrated therapy aimed at controlling all these risk factors is a critical aspect of type 2 DM management.³² Although studies such as Steno-2 validate multimetabolic approaches to management, the initial focus of DM management is glycemic control.³² The Steno-2 trial (N=160) demonstrated the benefits of this integrated approach by using a multifactorial intervention that showed that tight glycemic control has a modest effect on CVD risk, targeted hyperglycemia, hypertension, and dyslipidemia. The results of the trial showed a significant reduction in cardiovascular mortality (57% risk reduction; $P=.04$), death from any cause (46% risk reduction; $P=.02$), and a reduction in the risk of cardiovascular events (59% risk reduction; $P<.001$) in patients with type 2 DM (Figure 2),¹⁴ even though the patients in the intensive care group did not achieve target goals in all metabolic areas.^{14,33}

Treatment guidelines and results from multiple clinical landmark trials support the importance of moving beyond glycemia to fully address complications in patients with type 2 DM.^{15,34} Consideration of overall cardiovascular risk

may also include examining the selection of glucose-lowering strategies and their effect on overall CVD treatment; however, therapeutic choice should always be made on the basis of glycemic effect, metabolic risk, and mechanism of action.^{15,34} Older oral antidiabetes drugs effectively decrease hyperglycemia but, in the case of sulfonylureas and insulin, especially in the setting of ineffective lifestyle modification, frequently affect body weight, adversely leading to difficulty with glycemic control.³⁵ Sulfonylureas may be linked to increased CVD risk; however, it is unclear whether this is a direct drug effect, a marker of increased event rate due to hypoglycemia, or reflective of a waning legacy effect with declining diabetic control with these agents.³⁶ The weight gain seen with thiazolidinediones can be troubling but, unlike other agents, is not associated with a decrement in glycemic control and is linked to an improvement, not a worsening, of metabolic risk. However, thiazolidinediones have been associated with an increased risk of congestive heart failure and, in the case of rosiglitazone, a slightly increased risk of CVD. Weight gain with these agents is often a marker of volume expansion, and this needs to be clinically assessed against the important background of risk of congestive heart failure. Recent data also suggest that thiazolidinediones may decrease visceral abdominal fat production and increase subcutaneous and femoral fat production. Pioglitazone was shown to redistribute fat from visceral to subcutaneous depots, possibly suggesting a mechanism of action for the thiazolidinediones.³⁷ Nevertheless, there may be a potential modest CVD risk reduction with pioglitazone which was suggested in the PROspective pioglitazone Clinical Trial in macro Vascular Events (PROactive 10) and in subsequent safety meta-analyses.^{38,39} Thiazolidinedione use has also been associated with bone fractures, possibly more so in women than in men. Fractures of the hip or femur, humerus, and wrist or forearm were increased relative to nonuse of thiazolidinediones.⁴⁰

In contrast to other therapies, incretin-based treatments have shown at least short-term cardiovascular safety to date,⁴¹ and glucagon-like peptide 1 (GLP-1) analogues, such as exenatide and liraglutide, have shown positive effects on cardiovascular risk factors beyond hyperglycemia; however, no outcome data yet exist for this class of agents. Treatment with GLP-1 receptor agonists is consistently associated with reductions in body weight in at least half of patients treated with these agents, whereas dipeptidyl peptidase 4 (DPP-4) inhibitors are generally weight neutral.⁴² In patients with type 2 DM, GLP-1 receptor agonists decrease BP and improve the plasma lipid profile, and this effect appears to be independent of effects on weight.⁴³ Dipeptidyl peptidase 4 inhibitors do not affect BP and serum lipids to any substantial degree.⁴² Glucagon-like peptide 1 receptor agonists may have beneficial mechanistic effects on en-

FIGURE 2. Cumulative incidence of the risk of death and the composite end point of cardiovascular events, including death from cardiovascular causes, nonfatal stroke, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, revascularization for peripheral atherosclerotic disease, and amputation. Reprinted from *N Engl J Med*,¹⁴ with permission from the Massachusetts Medical Society.

dothelial and myocardial function, but the clinical effect on cardiovascular outcomes has yet to be investigated.⁴⁴⁻⁴⁸

IMPROVED CLINICAL OUTCOMES

The definitions of treatment success mentioned previously might be considered as surrogates for, or predictors of, improved clinical outcomes (eg, lack of microvascular and macrovascular complications) in patients with type 2 DM. Clinical trials have clearly shown the benefits of aggressive glucose-lowering therapy in delaying or preventing onset of DM complications, supporting the validity of this approach.^{4,32}

However, there are practical issues with using the presence or absence of complications as a definition of treatment success. Although these complications may be most readily apparent in patients with long-standing DM, vascular complications are evident in many individuals at the time of or before diagnosis of DM and before treatment is initiated.⁴⁹⁻⁵¹ Results from the Nurses Health Study, which included 117,629 female nurses aged 30 to 55 years, showed an increased risk of cerebrovascular disease and CVD before a clinical diagnosis of type 2 DM (Figure 3), which was not attributed to other factors, such as hypertension or dyslipidemia.⁵² Another epidemiological

FIGURE 3. Multivariate relative risks for myocardial infarction (MI) or stroke according to diabetes status: the Nurses Health Study, 1976-1996. Reprinted from *Diabetes Care*,⁵² with permission from the American Diabetes Association.

study indicated that young adults with early-onset type 2 DM have a higher risk of CVD than do age-matched controls.⁵³

Another disadvantage of judging the success of therapy according to clinical outcomes is the need for long-term observation. The benefit of tight glycemic control in decreasing the risk of macrovascular complications of DM was shown in the UKPDS, which included 5102 patients with newly diagnosed type 2 DM, 4209 of whom were randomly assigned to receive either conventional treatment (dietary restriction) or intensive therapy (a sulfonylurea or insulin or, in overweight patients, metformin) for glucose control. A 10-year follow-up of these patients indicated that intensive treatment was associated with significant reductions in the risks of any DM-related end point (9.0%; $P=.04$), microvascular disease (24%; $P=.001$), MI (15%; $P=.01$), and death from any cause (13%; $P=.007$).⁵⁴

Although it is agreed that controlling hyperglycemia reduces the incidence of complications due to DM, selection of target HbA_{1c} goals for specific patients is not straightforward. Results from several recent studies have suggested that tight glycemic control to near-normal values may not benefit all patients or extend to all treatment regimens. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized 10,251 patients with type 2 DM to comprehensive, intensive therapy with a target HbA_{1c} level less than 6% or conventional treatment with an HbA_{1c} goal of 7.0% to 7.9%. Study results showed that intensive therapy achieved an average HbA_{1c} level of 6.4% vs 7.5% for conventional treatment. However, compared with standard therapy, intensive treatment was associated with a significantly increased risk of death from any cause ($P=.04$), cardiovascular mortality ($P=.02$), and nonfatal MI ($P=.004$).⁵⁵ The overall death rate in both groups was con-

siderably lower than that seen in a conventionally treated diabetic cohort.

Two other recent studies, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release and Controlled Evaluation (ADVANCE) trial and the Veterans Administration Diabetes Trial (VADT), also indicated that intensive antidiabetes therapy does not decrease cardiovascular mortality or events in patients with DM.^{56,57} ADVANCE found a significant 14% reduction in microvascular outcome ($P=.01$) but no significant decrease in macrovascular outcome in intensively treated patients ($P=.32$). In VADT, the primary outcome, a composite of CVD events, was not significantly lowered in the intensive treatment arm ($P=.12$).

A meta-analysis of recent clinical outcomes studies in patients with type 2 DM indicated that intensive glucose control reduced the risk of some cardiovascular events (ie, nonfatal MI) but did not reduce either all-cause or cardiovascular mortality. Efforts to explain this limited benefit have focused on hypoglycemia and the influence of baseline patient characteristics on treatment outcomes. The risk of severe hypoglycemia increases in intensively treated patients,^{58,59} and this may have contributed to the mortality observed in studies that evaluated the benefits of intensive glucose control.⁶⁰

The American Diabetes Association, American Heart Association, and American College of Cardiology recently evaluated the results from ACCORD, ADVANCE, and VADT and how they may affect treatment recommendations for patients with DM. This analysis indicated that intensive glucose lowering may be unsuitable for all patients but that a subset of individuals with type 2 DM derives benefit from intensive therapy. Intensive glycemic control provided benefit by decreasing macrovascular complications in patients with a shorter duration of type 2 DM and without established atherosclerosis. In the ACCORD trial, patients with no prior CVD experienced a substantial reduction in cardiovascular events,⁶⁰ whereas patients with a long duration of DM, a history of hypoglycemia, and advanced atherosclerosis may not derive significant benefit from intensive antidiabetes therapy as noted in ACCORD, ADVANCE, and VADT.⁶⁰

Similarly, intensive treatment in a prespecified group of VADT patients with low baseline coronary artery calcium scores (0-100) resulted in a significantly lower risk of the primary end point (time to first occurrence of any of a composite of CVD events, including documented MI; cerebrovascular accident; cardiovascular death; new or worsening congestive heart failure; surgical intervention for cardiac, cerebrovascular, or peripheral artery disease; inoperable coronary artery disease; and amputation for ischemic gangrene) ($P=.03$).⁶¹

A review of results from ACCORD, ADVANCE, and VADT by the American Diabetes Association, American Heart Association, and American College of Cardiology reaffirmed an HbA_{1c} treatment goal of less than 7% for patients with DM. Both the Diabetes Control and Complications Trial and the UKPDS suggest that initiation of therapy aimed at lowering the HbA_{1c} level to less than 7% soon after the diagnosis of the disease decreases the risk of macrovascular complications.⁶⁰ This evaluation of landmark clinical end point trials also supports the view that treatment should be individualized for patients with type 2 DM, with more aggressive, early targets potentially appropriate in the younger diabetic patient and standard goals for the patient with established type 2 DM in whom CVD is already or likely to be present.

DURABILITY OF TREATMENT EFFICACY

Clinicians should consider both short- and long-term treatment outcomes when deciding what constitutes treatment success for their patients with DM. Declining β -cell function is the predominant factor in the deterioration of glucose tolerance that leads to type 2 DM^{24,35} and cascades into diabetic complications. Therefore, achieving sustained glycemic lowering over time (glycemic durability) is an important aspect of therapy that is not achieved in many patients treated with conventional oral agents.⁶² Reduction of the lipotoxicity associated with overweight/obesity is also inadequately addressed. However, determination of specific interventions and associated mechanisms for achieving durable glycemic control and their relation to the prolongation of β -cell function, slowed apoptosis, neogenesis, and/or other metabolic processes remains elusive.

PARADIGM SHIFT: FROM THE TRADITIONAL STEPPED-CARE APPROACH TO A STAGE-DEPENDENT INDIVIDUALIZED APPROACH

Historically, treatment approaches have been based on misunderstandings about the state of β -cell health and the duration of disease necessary before complications occur. Traditional treatment of DM has focused on reducing hyperglycemia in patients who may have already developed complications, which has led to a “one-size-fits-all” model of treatment. This approach follows a sequence in which treatment is intensified as β -cell dysfunction and death progress and insulin secretion decreases. Initial treatment recommendations call for lifestyle modification (diet and increased exercise), which typically is followed by the use of one or more oral antidiabetes drugs and, finally, by insulin therapy.⁶³ Generally, patients do not achieve durable glycemic control with this approach, and the underlying pathophysiology of the disease is not adequately addressed.³⁵

The described stepped-care approach is usually ineffective for long-term preservation of β -cell function and fails to recognize that treatment must be individualized because the rate of progression of type 2 DM may vary considerably. In addition, this stepped-care approach fails to recognize the advanced state of disease at diagnosis, the presence of both severe insulin resistance and β -cell dysfunction, and the relative weakness of a single therapy to address any physiologic defect adequately. A new treatment paradigm for the diagnosis and treatment of type 2 DM must address the multiple defects present and the patient’s stage of disease and then attempt to match therapeutic inadequacies with physiologic barriers in an individual patient.

MORE AGGRESSIVE DIAGNOSIS AND EARLY TREATMENT

Early diagnosis of patients with type 2 DM and even those with impaired glucose tolerance (IGT) is important because aggressive intervention at these stages can considerably alter the natural history of the disease, presumably by preserving β -cell function and reducing the development of complications. A growing body of evidence supports early and aggressive treatment initiation with a combination of antidiabetes agents that have the potential to alter the long-term course of type 2 DM.

Aggressive lifestyle intervention, metformin, and thiazolidinediones have been shown to delay progression to type 2 DM. In the preliminary results of the Diabetes Prevention Program Outcomes Study, 2766 individuals at high risk of developing DM were treated with intensive lifestyle intervention, metformin, or placebo. After 2.8 years of follow-up, intensive lifestyle intervention reduced the incidence of DM by 58% vs 31% with metformin compared with placebo. During the 10-year follow-up, the incidence of DM was reduced by 34% with the intensive lifestyle intervention and by 18% with metformin compared with placebo.⁶⁴ Additional data have shown that metformin therapy in patients with IGT can significantly delay progression to type 2 DM (35.5% risk reduction; $P < .0001$), although as shown in the Diabetes Prevention Program Outcomes Study, this was less than had been reported with aggressive lifestyle management.⁶⁵

In the ACTos NOW for the Prevention of Diabetes (ACT NOW) Study, 602 patients with IGT were randomized to receive pioglitazone or placebo and followed up for up to 4 years. Pioglitazone therapy resulted in a highly significant 81% relative risk reduction of developing DM ($P < .00001$) compared with placebo.⁶⁶ The Pioglitazone In Prevention Of Diabetes (PIPOD) study was an open-label, observational study in Hispanic women (N=86) with prior gestational DM who had completed participation in the TRoglitazone In Prevention Of Diabetes (TRIPOD) study. β -Cell function, insulin resistance, and the incidence of DM were

evaluated. Results showed that pioglitazone was able to stabilize β -cell function (stopping the decline in β -cell function that occurred in women from TRIPOD who subsequently were given placebo), increased insulin sensitivity, and decreased the rate of development of DM. The annual rate of development of DM was 4.6% compared with 12.1% observed during placebo treatment in TRIPOD.⁶⁷ Similar data have been reported in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial, suggesting that rosiglitazone significantly reduced the incidence of type 2 DM (hazard ratio, 0.40; $P<.0001$) and increased the likelihood of a return to normoglycemia in adults with impaired fasting glucose, IGT, or both.⁶⁸ Because an estimated 50% to 80% of normal β -cell function is lost at the time of type 2 DM diagnosis, early diagnosis and initiation of β -cell–modulating treatment afford the greatest opportunity to preserve remaining β cells.^{35,42}

Identification and aggressive treatment of younger patients with type 2 DM have the greatest potential for long-term benefit in disease modification and risk reduction, but the ratio of positive to negative screening test results can be expected to be low in this population. Screening patients who are aged 60 years or older is likely to increase the percentage diagnosed as having type 2 DM, but the benefits of aggressive treatment with respect to added life-years per patient and cost-effectiveness will not be as great as in younger patients, and addressing CVD risk in these patients may likely be of greater outcome benefit.⁶⁹ Furthermore, there are risks associated with aggressive treatment of the prediabetes condition, including weight gain and hypoglycemia, and these factors should be considered on a patient-by-patient basis.⁶⁴⁻⁶⁶

INNOVATIVE APPROACHES TO TYPE 2 DM MANAGEMENT

A growing body of evidence supports early and aggressive treatment initiation with a combination of antidiabetes agents that have the potential to alter the long-term course of type 2 DM. Historically, treatment approaches have lagged because of misunderstandings about the state of β -cell health and the duration of disease necessary before microvascular complications occur. Traditional views held that microvascular complications develop after approximately 10 years of type 2 DM, leading to a more leisurely approach to intensification of glycemic management. However, Kim et al⁷⁰ reported the presence of microalbuminuria (urinary albumin excretion rate of 20-200 $\mu\text{g}/\text{min}$ [to convert to grams per minute, divide by 10^5]) in 6.0% of healthy patients, 11.8% of patients with IGT, and 21.8% of patients with type 2 DM. Franklin et al⁷¹ showed that sensory peripheral neuropathy was evident in 3.9% of controls, 11.2% of patients with IGT, and 25.8% of patients

with type 2 DM. Data from NHANES 1999-2002 show that nephropathy and peripheral neuropathy were present in 24.9% and 21.5% of patients with undiagnosed type 2 DM, respectively, and in 28.0% and 19.2% of patients with diagnosed DM, respectively.⁷²

Finally, in the MONItoring of trends and determinants in CARdiovascular disease (MONICA)/Cooperative Health Research in the Region of Augsburg (KORA) surveys, the prevalences of polyneuropathy in patients with DM, IGT, impaired fasting glucose, and normal glucose tolerance were 28.0%, 13.0%, 11.3%, and 7.4%, respectively ($P<.05$ for DM vs normal glucose tolerance, impaired fasting glucose, and IGT).⁴⁹

It is evident that macrovascular disease may start much earlier as well, yet current metabolic risk guidelines do not intensify targets in the patient with IGT.^{4,73} Hu et al⁵² and Ingelsson et al⁷⁴ demonstrated the presence of subclinical CVD in patients with metabolic syndrome or DM and an increased risk of CVD before their diagnosis.

Metabolic memory is a term used to describe the beneficial effects of immediate intensive treatment of hyperglycemia (reducing both microvascular and macrovascular complications) and the continuation of these benefits for many years, regardless of glycemia later in the disease. Clinical trials have now confirmed the observation first seen in pre-clinical models.^{54,75} In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study, 1441 patients with type 1 DM were randomized to intensive therapy or standard therapy for a mean of 6.5 years. Baseline HbA_{1c} level was 9.1% in both groups and at the end of 6.5 years was 7.4% and 9.1% in the intensive and standard therapy groups, respectively. A total of 93% of patients were followed up observationally for a mean of 17 years, after which intensive therapy significantly reduced the risk of any cardiovascular event by 42% ($P=.02$) and the risk of nonfatal MI, stroke, or death from CVD by 57% ($P=.02$), despite the convergence of HbA_{1c} at the end of the 17-year follow-up (7.9% and 7.8%, respectively).⁷⁵

In UKPDS 80, 4209 patients with newly diagnosed type 2 DM were randomized to receive intensive therapy with a sulfonylurea or insulin or metformin or standard therapy and were followed up for 10 years. Mean HbA_{1c} level at the end of the study was significantly lower in both intensive therapy groups ($P<.001$). Patients were then enrolled in the posttrial monitoring program and followed up in the clinic for 5 years and for an additional 5 years with surveys. Between-group differences in HbA_{1c} levels were lost after the first year of posttrial follow-up. Despite this, in the sulfonylurea or insulin intensive therapy group, relative reductions in risk persisted at 10 years for any DM-related end point (9%; $P=.04$) and microvascular disease (24%; $P=.001$), and

risk reductions for MI (15%; $P=.01$) and death from any cause (13%; $P=.007$) emerged over time. Substantial risk reductions were also seen in the metformin intensive therapy group.⁵⁴ This is known as the *legacy effect*.⁷⁶

SELECTION AND TIMING OF ANTIDIABETES AGENTS FOR GLYCEMIC CONTROL

Antidiabetes agents that reduce peripheral insulin resistance have the potential to spare the β cell from premature exhaustion during early type 2 DM.^{35,77} The β -cell–modulating effects of thiazolidinedione therapy act considerably in this regard. The relatively lesser effects of metformin on peripheral insulin resistance are likely the reason it has only modest effects on β -cell function and durability of glycemic response.

Incretin-based therapies, such as GLP-1 receptor agonists and DPP-4 inhibitors, which prevent the breakdown of GLP-1 and thus prolong its duration of action, have the potential to address β -cell functioning and mass and the durability of glycemic effects through novel mechanisms of action.⁷⁸ Although GLP-1 receptor agonists and DPP-4 inhibitors have yet to show the ability to increment β -cell mass in patients with type 2 DM, they have demonstrated this effect in animal models of DM and have been shown to improve β -cell function in human clinical trials, with some evidence of sustainability of effect.^{43,78}

The stage of type 2 DM at diagnosis should also affect the selection of agents for optimal disease management.^{32,42} Agents that have properties with the potential to modify the course of disease should be considered for early use, before sustained elevations of glucose and lipid levels have resulted in a nearly complete loss of β -cell mass and function.^{32,35,42} Durable reductions in plasma glucose values may be more easily achieved when there is a larger β -cell mass and a potential pool of recoverable and differentiated β cells.^{32,35}

COMBINATION THERAPIES FOR GLYCEMIC CONTROL

Initial aggressive antidiabetes therapy is likely to include multiple agents and regimens. Regimens should include medications with complementary mechanisms of action that act additively or perhaps even synergistically against multiple disease mechanisms.^{17,35} For example, a possible combination of metformin to provide suppression of hepatic glucose production; pioglitazone, a thiazolidinedione, to improve insulin sensitivity; and exenatide, a GLP-1 receptor agonist, to preserve and enhance β -cell function would address 3 fundamental defects, although the superiority of this aggressive “top-down” therapeutic approach has yet to be validated in an outcomes trial.^{17,35} Interestingly, a recent open-label study evaluated the effects of adding the GLP-1 receptor agonist exenatide or the thiazolidinedione rosiglitazone, or both, on insulin secretion, insulin sensi-

tivity, and β -cell function in 73 patients with type 2 DM. Patients' conditions were inadequately controlled (mean HbA_{1c} level, 7.8%) but were maintained with a stable dose of metformin for at least 6 months before screening. Insulin resistance was measured by the euglycemic insulin clamp technique, and β -cell function was measured by the disposition index (derived by the hyperglycemic and euglycemic clamps). The HbA_{1c} level decreased from baseline in all groups ($P<.05$) but decreased most with exenatide plus rosiglitazone. First- and second-phase insulin secretion was improved significantly from baseline with exenatide and exenatide-rosiglitazone ($P<.05$) but not with rosiglitazone alone. Exenatide and exenatide-rosiglitazone but not rosiglitazone alone were found to significantly improve β -cell function ($P<.001$). Rosiglitazone and exenatide-rosiglitazone but not exenatide alone significantly improved insulin sensitivity ($P<.05$).⁷⁹ Nausea was the most common adverse event in patients receiving exenatide (47%) and in those receiving exenatide with rosiglitazone (47%). Vomiting occurred in 22% of patients receiving exenatide and in 19% of patients given exenatide and rosiglitazone. Two patients given exenatide discontinued use of the drug because of nausea, whereas 2 patients given exenatide and rosiglitazone stopped taking the drugs because of nausea and 1 stopped because of vomiting. Pedal edema was the most common adverse event in patients receiving rosiglitazone, with 1 patient discontinuing use of the drug because of peripheral edema.⁷⁹ In summary, glycemic improvement in these patients was due to significant improvements in insulin sensitivity and therefore β -cell workload, as well as improved β -cell function, 2 of the major core defects associated with type 2 DM.⁷⁹ Whether this mechanistically attractive but costly treatment paradigm will lead to more effective long-term diabetic control with more favorable outcomes remains to be seen.

CONCLUSION

Clinicians must recognize that DM is a progressive disease and that treatment strategies must be dynamic and proactive rather than reactive because each sustained increase in HbA_{1c} level is reflective of worsening physiologic mechanisms. Durability of glucose control is as important as achievement of glycemic control in defining success because it reflects a slowing or stabilization of the disease process. To achieve successful clinical outcomes in patients with type 2 DM, a multitude of factors must be addressed, including mechanisms of disease and complications, achievement of durable glycemic control, and decreasing risk of microvascular and macrovascular complications through aggressive multiple metabolic management. The concept of metabolic memory suggests that the

earlier in the disease stage this is achieved, the greater the potential long-term outcome benefit. A multi-interventional strategy that targets glycemic control, as well as other risk factors such as hypertension, overweight/obesity, and dyslipidemia, is not novel in type 2 DM. However, earlier and more aggressive implementation of existing strategies, especially in patients with markers of higher risk, has the potential to provide the greatest reductions in morbidity and mortality in this patient population and lead to long-term treatment success.

CLINICAL PEARLS

- Because type 2 DM is a pathophysiologically complex disease, successful antidiabetes therapies must address β -cell dysfunction, insulin resistance, adipocyte dysfunction, and ultimately insulin deficiency.
- Treatment success in type 2 DM extends beyond reaching glycemic targets and must address durability of glycemic control and favorable long-term clinical outcomes.
- In patients with type 2 DM, CVD is the primary cause of mortality, and all cardiovascular risk factors must be lowered to reduce the high mortality and morbidity in this population.
- Successful HbA_{1c} targets should be based on the individual's age and duration of DM, with more intensive therapy early in the disease.

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