Oversight of Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus (DM2) is an increasingly prevalent condition that is associated with many complications, the most serious of which is cardiovascular disease (CVD). Patients with DM2 may also have hypertension and/or dyslipidemia, which are overlapping risk factors for CVD. Therefore, good glucose, blood pressure (BP), and lipid control are essential in preventing cardiovascular events. Appropriate management should be based on the most recent American Diabetes Association guidelines, as well as current BP (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) and cholesterol (Adult Treatment Panel III) guidelines. Understanding antidiabetic agents, their place in treatment, and a stepwise treatment approach are critical to appropriate medication management. Recent diabetic clinical trial results may guide future treatment strategies in the management of patients with DM2.

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Diabetes mellitus (DM) is a group of metabolic conditions characterized by hyperglycemia secondary to defects in insulin production or utilization.1 Type 2 DM (DM2) is caused by resistance to insulin action on target tissues and inadequate insulin secretion in reaction to diminished tissue response.1 When insulin resistance occurs, insulin requirements increase. However, dysfunction of pancreatic β cells results in inadequate insulin secretion and the inability to compensate for increased insulin demand. Consequently, hyperglycemia ensues, and symptoms, such as lethargy, polyuria, polydipsia, and polyphagia, may occur when blood glucose levels become very high.1 Because hyperglycemia in DM2 may be asymptomatic, individuals could remain undiagnosed until serious complications develop.1

The Growing Prevalence of DM2

The prevalence of DM2 is increasing in modern US society. As of 2007, 23.6 million Americans were diagnosed with DM, with DM2 accounting for 90% to 95% of these cases.2 Of this 23.6 million, 23.5 million Americans were 20 years or older (representing 10.7% of the total population of this age group) and 12.2 million Americans were 60 years or older (representing 23.1% of the total population of this age group).2 From 1990 to 2005, the prevalence of DM has increased at a rate of roughly 5% annually, a figure that is expected to escalate.3

The upsurge in the number of Americans with DM over the last 2 decades appears to be associated with the increasing rate of obesity. The risk of death among individuals with diabetes is approximately twice that of individuals without the condition who are of similar age.2 Although DM2 was once considered a disease of adults, the incidence is increasing among children and adolescents as more younger Americans become overweight.5

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**RISK FACTORS AND COMPLICATIONS**

To prevent complications associated with DM2, appropriate screening is important to detect and treat hyperglycemia early and to detect complications before they become too advanced. General population screening of all individuals for diabetes is generally not advocated because screening of high-risk individuals may be more cost effective. All asymptomatic adults who are overweight or obese (body mass index ≥25 kg/m²) and who have 1 or more additional risk factors should be tested for diabetes. In adults without risk factors, testing should begin at age 45 years. Risk factors include habitual physical inactivity; family history of DM in a first-degree relative; high-risk ethnicity (African American, Latino, Native American, Asian American, and Pacific Islander); history of gestational DM or delivery of a baby greater than 9 lbs; hypertension (HTN; ≥140/90 mm Hg or on antihypertensive medication); high-density lipoprotein cholesterol level less than 35 mg/dL or a triglyceride level greater than 250 mg/dL; polycystic ovarian syndrome (PCOS); impaired fasting glucose or impaired glucose tolerance on previous testing; history of vascular disease; and severe obesity. Asymptomatic children should be screened if they are overweight and have 2 additional risk factors. Risk factors for children include family history of DM2 in a first- or second-degree relative; high-risk ethnic groups; conditions associated with insulin resistance (HTN, dyslipidemia, obesity, and PCOS); and maternal history of DM.

Left untreated, patients with DM2 are at risk for developing microvascular and macrovascular complications in addition to infections (eg, influenza and pneumonia). Microvascular complications include neuropathy (eg, diabetic foot infections), retinopathy, and nephropathy, whereas macrovascular complications include cardiovascular disease (CVD), peripheral arterial disease, and stroke. Screening for complications includes regular physical examinations, foot evaluation, annual retinal examination, and laboratory tests for lipid abnormalities and microalbuminuria.

Cardiovascular disease is the primary cause of morbidity and mortality among patients with diabetes. HTN and dyslipidemia are common comorbid conditions that not only increase the risk of developing DM2 but also are independent risk factors for CVD. HTN is also linked to diabetic retinopathy and nephropathy, which could progress to end-stage renal disease. Large trials involving patients with DM have found that aggressive control of blood pressure (BP) improves cardiovascular outcomes as well as retinopathy and nephropathy. In addition to lifestyle changes for dyslipidemia, studies have shown that lipid-lowering therapy may prevent CVD in patients with DM and may improve outcomes in patients with DM and coronary heart disease. Smoking cessation is recommended for patients with DM2 because cigarette smoking contributes to dyslipidemia and cardiovascular risk.

**DIAGNOSIS AND GOALS OF TREATMENT**

Three diagnostic tests are used to detect DM2. A fasting plasma glucose (FPG) of 126 mg/dL or higher, a random plasma glucose of 200 mg/dL or higher with symptoms of hyperglycemia, or a 2-hour plasma glucose (2-h OGTT) of 200 mg/dL or higher during an oral glucose tolerance test are all indicative of DM2. Each of these findings must be confirmed on a second occasion unless the individual presents with irrefutable symptoms of hyperglycemia. In patients who are prediabetic or asymptomatic, either FPG testing or 2-h OGTT is appropriate.

Glycemic control is a strong predictor of adverse outcomes. Glycosylated hemoglobin (A1c) is a primary measure of glycemic control, with a target of less than 7% in individuals with DM. Additionally, glycemic control may be assessed through patient self-monitoring of blood glucose, with recommended levels for preprandial plasma glucose and peak postprandial plasma glucose levels being 70 to 130 mg/dL and less than 180 mg/dL, respectively.

**PHARMACOTHERAPEUTIC CLASSES**

The American Diabetes Association recommendations for metabolic management of DM2 are shown in Figure 1.

**BIGUANIDES**

Metformin is a biguanide that decreases hepatic glucose production and increases glucose uptake by muscles. Because metformin is at minimum weight neutral, can promote weight loss in some individuals, can improve lipid profiles, and can reduce macrovascular complications, it may be beneficial as a first choice for overweight/obese individuals. Rare lactic acidosis is a serious and sometimes fatal adverse event associated with metformin. Symptoms include muscle pain, weakness, dizziness, and bradycardia. Risk factors for lactic acidosis include renal or hepatic dys-
function, alcohol use, radiocontrast dye, and severe congestive heart failure (CHF).9

**INSULIN**

Insulin is the most effective antidiabetic agent available for lowering blood glucose.8 Expected A1c reduction is 1.5% to 3.5%; however, target A1c can almost always be reached when insulin is used in sufficient doses.8 To overcome insulin resistance, larger doses of insulin (≥1 U/kg), with or without an insulin sensitizer and lifestyle changes, must be used in DM2.8 Intermediate- and long-acting insulins are used to increase basal insulin levels, whereas short- and rapid-acting insulins may be required for postprandial glucose control.8,9 Adverse events associated with insulin include weight gain and hypoglycemia.8

**SULFONYLUREAS**

Sulfonylureas lower blood glucose by stimulating pancreatic β cells to produce insulin.9 Commonly prescribed agents include the second-generation sulfonylureas, such as glipizide, glyburide, and glimepiride. Glipizide is the preferred agent in patients with renal impairment. Sulfonylureas possess some insulin-sensitizing effects, and glimepiride is indicated for use with insulin.9 Sulfonylureas should be taken no more than 30 minutes before a meal and should not be taken at all if a meal is skipped. Typical dosage and expected A1c reductions (Table 1) and side effects (Table 2) for antidiabetic agents are summarized below.8,9 Dose titration can minimize side effects for some agents.

**D-PHENYLALANINE AND MEGLITINIDE DERIVATIVES**

Meglitinide and D-phenylalanine derivatives (repaglinide and nateglinide, respectively) stimulate insulin secretion from pancreatic β cells. Due to their short duration of action, the risk of hypoglycemia is less than with sulfonylureas. These agents are short acting and should be dosed with each meal.9 They are approved as monotherapy or in combination with metformin or a thiazolidinedione (TZD).9

**THIAZOLIDINEDIONES**

Thiazolidinediones, such as pioglitazone and rosiglitazone, increase glucose uptake in the muscle, liver, and periphery and increase insulin sensitivity.9 These agents are approved as monotherapy or in combination with metformin, sulfonylureas, or insulin. TZDs should be avoided or discontinued in patients with severe CHF or hepatic disease.9 A recent meta-analysis, whose findings are currently under US Food and Drug Administration (FDA) review, found that rosiglitazone may be associated with increased risk of myocardial infarction (P = .03) and death from cardiovascular causes (P = .06).9,11 However, this risk has not been observed in large long-term clinical trials. In addition, pioglitazone decreased the risk of myocardial infarction, stroke, and death in the PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial but did not reduce the composite of all cardiovascular events significantly.12

**α-GLUCOSIDASE INHIBITORS**

Acarbose and miglitol are α-glucosidase inhibitors that delay the breakdown of carbohydrates in the small intestine, thereby slowing carbohydrate absorption. Thus, these agents should be taken just before meals.9
When used as monotherapy, these agents are minimally effective and decrease the A1c by 0.5% to 0.8%. Therefore, their use in combination with metformin, sulfonylureas, or insulin may be more useful. In the event of hypoglycemia, patients should be treated with glucose rather than complex carbohydrates, which are not broken down by α-glucosidase inhibitors. Side effects, including flatulence and abdominal discomfort, are frequent, and often limit the use of these drugs.

**INCRETIN-RELATED AGENTS**

Glucagon-like peptide-1 (GLP-1) is a natural gut peptide that stimulates insulin secretion (incretin effect) and suppresses glucagon. Because of its very short half-life, its degradation must be blocked, or a

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**Table 1. Dosing of Antidiabetic Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Reduction in A1c in Trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide</td>
<td>IR: 2.5–20 mg daily or BID; maximum 40 mg/day</td>
<td>1%–2%</td>
</tr>
<tr>
<td></td>
<td>XL: 2.5–10 mg daily or BID; maximum 20 mg/day</td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>Regular: 1.25–5 mg daily or BID; maximum 20 mg/day</td>
<td>1%–2%</td>
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<tr>
<td></td>
<td>Micronized: 0.75–12 mg/day</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1–8 mg/day</td>
<td>1%–2%</td>
</tr>
<tr>
<td>Metformin</td>
<td>IR: 500 mg BID with meals; increase by 500 mg every 1–3 weeks; most effective at 2000 mg/day; maximum 2550 mg/day</td>
<td>1%–2%</td>
</tr>
<tr>
<td></td>
<td>XR: 500 mg once daily; maximum 2000 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>New diagnosis or A1c &lt;8%: 0.5 mg before each meal</td>
<td>1%–1.5%</td>
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<tr>
<td></td>
<td>A1c &gt;8%: 1–2 mg before each meal</td>
<td></td>
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<tr>
<td></td>
<td>May increase weekly to a maximum of 16 mg/day</td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60–120 mg before each meal</td>
<td>1%–1.5%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>15 or 30 mg daily; maximum 45 mg daily for monotherapy and 30 mg</td>
<td>0.5%–1.4%</td>
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<tr>
<td></td>
<td>daily for combination therapy</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4 mg/day in single or divided doses; increase to 8 mg/day in 12 weeks</td>
<td>0.5%–1.4%</td>
</tr>
<tr>
<td></td>
<td>if needed; maximum 8 mg/day</td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td>Initial 25 mg TID with meals; may increase to 50–100 mg TID with</td>
<td>Minimal; must be used in</td>
</tr>
<tr>
<td></td>
<td>maximum 300 mg/day (or 150 mg/day if &lt;60 kg)</td>
<td>combination therapy</td>
</tr>
<tr>
<td>Miglitol</td>
<td>Initial 25 mg TID with meals; may increase to 50 mg TID with meals;</td>
<td>Minimal; must be used in</td>
</tr>
<tr>
<td></td>
<td>maximum 100 mg TID with meals</td>
<td>combination therapy</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Initial 5 µg BID within 60 minutes prior to meals; after 1 month may</td>
<td>0.5%–1% in</td>
</tr>
<tr>
<td></td>
<td>increase to 10 µg BID</td>
<td>combination therapy</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Initial 60 µg prior to meals; may increase to 120 µg prior to meals</td>
<td>0.5%–1%</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg once daily; 50 mg once daily for CrCl 30–50 mL/min; 25 mg</td>
<td>0.5%–0.8%</td>
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<tr>
<td></td>
<td>once daily for CrCl &lt;30 mL/min</td>
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</table>

*The A1c reduction in trials is usually dependent on the baseline A1c and also the duration of the trial. A1c = glycosylated hemoglobin; BID = twice daily; CrCl = creatinine clearance; IR = immediate release; TID = 3 times daily; XL = extended release; XR = extended release.

Data from National Diabetes Education Program.

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**Table 2. Side Effects of Antidiabetic Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide, glyburide, and</td>
<td>Weight gain, hypoglycemia, and rare severe hypoglycemia</td>
</tr>
<tr>
<td>glimepiride</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Transient GI effects (nausea and diarrhea); rare lactic acidosis</td>
</tr>
<tr>
<td>Repaglinide and nateglinide</td>
<td>Hypoglycemia and weight gain</td>
</tr>
<tr>
<td>Pioglitazone and rosiglitazone</td>
<td>Weight gain, fluid retention, and worsening heart failure</td>
</tr>
<tr>
<td>Acarbose and miglitol</td>
<td>Hypoglycemia, abdominal cramping, bloating, flatulence, and diarrhea</td>
</tr>
<tr>
<td>Exenatide</td>
<td>GI effects (nausea and diarrhea) and dizziness</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Hypoglycemia, nausea, vomiting, and weight loss</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Headache, diarrhea, and upper respiratory tract infection</td>
</tr>
</tbody>
</table>

GI = gastrointestinal

Data from Nathan et al and National Diabetes Education Program.
long-acting analog must be used. The GLP-1 analog exenatide, a subcutaneous injectable agent, is an incretin-mimetic that enhances glucose-dependent insulin secretion and slows gastric emptying. It is approved as adjunctive therapy with metformin, a sulfonylurea, a TZD, or a combination of these agents. Adverse events include nausea, vomiting, and significant weight loss. Recently, the FDA has issued a warning concerning 6 reported cases of hemorrhagic necrotizing pancreatitis with recommendations to discontinue exenatide if pancreatitis is suspected.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that prolongs active incretin levels, resulting in increased insulin release from pancreatic β cells and decreased glucagon secretion from pancreatic α cells. It is approved as monotherapy or in combination with metformin or a TZD. Eighty-seven percent of the drug is eliminated in the urine, requiring dosage adjustment in renal impairment.

Several other GLP-1 analogs and DPP-4 inhibitors are in development.

**Amylin Analog**

Pramlintide is an amylinomimetic that prevents postprandial glucagon secretion, slows gastric emptying, and promotes satiety, leading to decreased caloric intake. It is approved for use only with concomitant insulin therapy, with or without metformin or sulfonylureas. Pramlintide is administered subcutaneously with each meal and with concurrent insulin dose reduction by 50% to avoid hypoglycemia.

**Initiating and Adjusting Diabetes Therapy**

Lifestyle interventions are a first step in managing new-onset DM2. Weight loss, physical activity, and smoking cessation improve glucose levels, BP, lipid levels, and thereby, reduce CVD risk. Metformin should be initiated at the time of diagnosis with dose titration in most patients. If hyperglycemia persists, the addition of other medications (ie, insulin, a sulfonylurea, or a TZD) may be considered. When combination therapy is necessary, agents with differing mechanisms of action have the most synergy. If the addition of a second agent does not produce adequate results, insulin therapy should be started or intensified. Although insulin intensification is preferred, addition of a third oral agent may be considered. Figure 2 describes insulin therapy initiation and adjustment.

**Diabetes Clinical Trial Results**

**ADOPT**

A Diabetes Outcome Progression Trial (ADOPT) evaluated the comparative efficacy of rosiglitazone (titrated up to 8 mg/day), glyburide (titrated up to 15 mg/day), and metformin (titrated up to 2 g/day) in drug-naïve patients with DM2 diagnosed in the previous 3 years. The primary outcome was the time to monotherapy failure, which was defined as an FPG greater than 180 mg/dL. Progression to hyperglycemia was slower in patients who received rosiglitazone than in those who were treated with metformin (32% risk reduction; P < .001) or glyburide (63% risk reduction; P < .001). However, significantly more patients on rosiglitazone experienced CVD, CHF, weight gain, and edema.
ACCORD

The Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD) includes adults with DM2 and at high risk for CVD. The trial assesses 3 medical treatment strategies aimed at reducing the rate of poor CVD outcomes in patients with DM2. The glycemia trial is designed to determine whether a target A1c of less than 6% will reduce the rate of cardiovascular events to a greater extent than a target A1c of 7% to 7.9%. The lipid trial is designed to evaluate whether fenofibrate in combination with a statin will reduce the rate of cardiovascular events to a greater extent than a statin alone in patients with good glycemic control. The BP trial is designed to determine if a target systolic BP of less than 120 mm Hg will reduce the rate of cardiovascular events to a greater extent than a target systolic BP of less than 140 mm Hg in patients with good glycemic control. The study is expected to be completed in 2009. At 1 year, mean A1c levels were 6.4% in the intensive therapy group and 7.5% in the standard therapy group. There was no difference in cardiovascular events between groups (P = .16), but significantly more patients in the intensive therapy group died (P = .04). The study was stopped early due to these deaths.

VADT

The Veterans Affairs Diabetes Trial (VADT) enrolled older patients with DM2 who were uncontrolled on their current regimens. Patients were randomized to receive intensive therapy (A1c <7%) or standard therapy. An A1c difference of at least 1.5% between the 2 groups was maintained, with a median A1c of 6.9% in the intensive therapy group and 8.4% in the standard therapy group. Both groups received glimepiride or metformin plus rosiglitazone, with the addition of insulin or other oral agents as necessary. The primary objective was to evaluate the effects of intensive glycemic treatment on cardiovascular outcomes. Investigators found no association between A1c reduction and macrovascular disease events. The lack of correlation could be due to the absence of intensive glucose control implementation closer to the time of diagnosis. The trial will continue as an observational study for another 9 years.

ADVANCE

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial is a factorial (perindopril plus indapamide [PD-ID] and gliclazide study treatments) trial designed to assess the effects on major vascular outcomes in patients with DM2 by: (1) lowering BP for patients with HTN; and (2) lowering A1c to 6.5% or less. In the first study arm, patients were randomized to receive either PD-ID or placebo along with intensive blood glucose control (target A1c ≤6.5%) or standard glucose control (target A1c based on local guidelines). In the second treatment arm, patients were randomized to receive: (1) intensive glucose control with gliclazide with sequential addition or increase in dose of metformin, TZDs, acarbose, or insulin based on A1c levels; or (2) standard control with a sulfonylurea other than gliclazide. In the first study arm, the active therapy group (PD-ID group) demonstrated a relative risk reduction in macrovascular or microvascular events of 9% (P = .04). Death from CVD was reduced by 18% (P = .03). In the second study arm, the mean A1c level was lower in the intensive control group (6.5% vs 7.3%). Intensive control reduced the incidence of combined vascular events (P = .01), major microvascular events (P = .01), and the incidence of nephropathy (P = .006). No significant effects were seen on major macrovascular events or death.

Thus, intensive control remains important to decrease the risk of microvascular events, but its role in prevention of macrovascular events is unclear. The latter are clearly not prevented over a 3- to 5-year period in patients whose BP and lipids are well controlled. Very tight and rapid control should probably be avoided in high-risk and older patients.

STENO-2

The Steno-2 Study evaluated the effect of intensified, targeted, multifactorial intervention versus conventional intervention for modifiable risk factors of CVD in patients with DM2 and persistent microalbuminuria. The primary end point was composite death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation. Intensive treatment targeted hyperglycemia, HTN, dyslipidemia, microalbuminuria, and secondary prevention of CVD with aspirin through a stepwise implementation of behavior modification and pharmacologic therapy. Conventional treatment was in accordance with national guidelines.

After a mean follow-up of 7.8 years, the intensive...
therapy group demonstrated a significantly greater decline in A1c values, systolic and diastolic BP, serum cholesterol and triglyceride levels, and urinary albumin excretion. The intensive therapy group also demonstrated a lower risk of developing CVD (hazard ratio, 0.47), nephropathy (hazard ratio, 0.39), retinopathy (hazard ratio, 0.42), and autonomic neuropathy (hazard ratio, 0.37). In a mean 13.3-year treatment follow-up study, the intensive therapy group demonstrated a 20% absolute risk reduction for death from any cause. The absolute risk of death from cardiovascular causes was decreased by 13%.  

**Multidisciplinary Team Approach**

Data from 1999 to 2000 showed that only 36% of patients with diabetes in the United States achieve the target A1c of less than 7%. Deficiencies in patient education may contribute to this lack of adequate glycemic control. The health professional team should reinforce with patients the importance of medication adherence and lifestyle modifications. Review of glycemic goals and the consequences of uncontrolled DM should be discussed. Education should include information about the importance of foot care, regular dental examinations, influenza and pneumococcal vaccinations, and infection control procedures. Dieticians and nutrition experts should discuss dietary recommendations for DM2, including healthy eating, exercise, and weight control. Pharmacists are essential to patient counseling about the indication, administration, and side effects of medications. The importance of glucose monitoring and the symptoms of hypoglycemia and its management should be discussed.

**Conclusions**

Type 2 DM is an increasingly prevalent condition associated with serious microvascular and macrovascular complications. With proper management, the risk of complications can be prevented or decreased. Future therapies for DM2 may include not only the development of new medications or delivery devices but also pharmacologic strategies to prevent or delay DM2. Strategies may include treatment with oral hypoglycemic agents, antiobesity drugs, statins, fibrates, estrogen, and antihypertensive agents. With knowledge of management guidelines, the multidisciplinary healthcare team can improve treatment regimens and optimize clinical outcomes.

**References**


