

# Current Therapeutic Algorithms for Type 2 Diabetes

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*Although type 2 diabetes is a heterogeneous disorder, there are certain management goals that are common to all patients. Tight metabolic control reduces the complication rates; therefore, for patients with type 2 diabetes, lowering the hemoglobin A<sub>1c</sub> toward normal is a major goal, as is the achievement of normal lipids and blood pressure. This article first discusses the standard regimens and agents available and then focuses on the newer approaches to reaching these goals.*

## MANAGEMENT OF TYPE 2 DIABETES MELLITUS

### Education

Education of the patient is the most critical element in the management of diabetes and frequently the most overlooked. Physicians often have limited time during office visits to educate patients regarding the disease, its cause and treatment, and the prevention of complications. Diabetes educators—both registered nurses and registered dietitians—are therefore excellent alternatives; the education they can provide to patients will lead to greater motivation and compliance and an improved outcome. Education should focus on lifestyle changes, home glucose monitoring, and the latest information regarding the prevention of complications, for example, the results of trials such as the Diabetes Control and Complications Trial (DCCT) (1) and the UK Prospective Diabetes Study (UKPDS) (2). **Table I** presents management goals that are common to all patients with type 2 diabetes. Treatment goals for type 2 diabetes are presented in **Table II**.

### KEY POINT

Education of the patient is the most critical element in diabetes management and should focus on weight reduction and lifestyle changes, home glucose monitoring, and keeping up to date on the prevention of complications.

### Diet

Because 60% to 80% of patients with type 2 diabetes are overweight, and obesity, even in individuals who are not diabetic, is universally associated with insulin resistance, the primary aim of diabetes therapy should be weight reduction. A number of popular diets have been publicized for weight reduction. Unfortunately, the long-term success rates of these diets are very low; >90% of patients at 1- to 2-year follow-ups have returned to their initial body weight and may even rebound to higher weights.

TABLE 1.

## MANAGEMENT GOALS FOR ALL PATIENTS WITH TYPE 2 DIABETES MELLITUS

- Education: diabetes nurse educator, home blood glucose monitoring, HbA<sub>1c</sub>
- Diet: nutritionist
- Exercise
- Oral agents
- Insulin
- Treatment of coexisting conditions
  - Antihypertensive therapy
  - Lipid-lowering agents

HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>.

A more appropriate technique for dietary weight loss is a less severe reduction in caloric intake over a more prolonged period with a change in lifestyle. Because 1 pound of body fat contains ~3500 kcal, a reduction of 300 to 400 kcal in daily caloric intake will result in a weight loss of almost 1 pound per week. A regimen that includes a minimal daily caloric requirement of 1500 kcal for women and 1800 kcal for men (depending on body weight) combined with an exercise program and some form of group or behavioral therapy would have probably the greatest chance of success. There is compelling evidence that increasing the intake of monounsaturated or polyunsaturated fats and decreasing saturated fats and using high fiber/low-glycemic index diets may prevent type 2 diabetes and improve insulin sensitivity in established diabetes (3).

Weight reduction in patients with type 2 diabetes is associated with the improvement of several metabolic parameters, including low plasma glucose and lipid levels as well as improved blood pressure measurements.

### Exercise

Exercise is recommended for lowering plasma glucose, lipid levels, and blood pressure. To achieve these goals, exercise should be performed every day for at least 30 minutes and may consist of either aerobic or anaerobic exercises.

It is recommended that older patients with type 2 diabetes who may already have complications—such as coronary disease, neuropathy, or retinopathy—should avoid sudden, strenuous exercise, thus avoiding sudden deterioration of these complications. For example, proliferative retinopa-

thy may be associated with hemorrhage, and neuropathy may be affected by uncontrolled exercise, resulting in soft tissue and joint injuries, and also may be associated with increased proteinuria. Therefore, patients with type 2 diabetes should undergo a thorough physical examination before beginning an exercise training program. In addition, these patients should be educated as to how to regulate their diet and medication while increasing their exercise routine. Self-monitoring of blood glucose plays an important role in assessing the blood glucose levels before, during, and after exercise, especially in very insulin-deficient patients with type 2 diabetes.

### KEY POINT

**For patients who do not achieve glycemic goals with lifestyle changes, there are now 5 major groups of medications that can be used to achieve glycemic control either alone in the early stage of the disease or in combination as the disease progresses.**

### CURRENT PHARMACOLOGIC THERAPY

Five major groups of medications are available to patients with type 2 diabetes: insulin secretagogues (sulfonylureas and nonsulfonylureas), biguanides, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, and insulin. Within each family there are numerous options; however, the mechanism of action of each compound within a particular group is generally similar.

TABLE II.

## TREATMENT GOALS FOR TYPE 2 DIABETES MELLITUS

Index Required	Target Levels (mg/dL)		
	Nondiabetic	Goal for Diabetics	Action
Preprandial glucose	<110	80–120	<80 or >140
Postprandial glucose	<140	<180	>180
Bedtime glucose	<120	100–140	<100 or >160
HbA <sub>1c</sub> (%)*	<6	<6.5	>7.5

\*American Diabetes Association guidelines for 2001 suggest a goal of <7% HbA<sub>1c</sub>. The European Association for the Study of Diabetes, the American College of Endocrinology, and the American Association of Clinical Endocrinologists suggest a goal of <6.5% HbA<sub>1c</sub>.

HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>.

### Insulin Secretagogues

**Sulfonylureas.** These agents have been available for almost half a century, but only recently have their mechanisms of action been characterized (4). They bind the sulfonylurea receptor (SUR) on the beta cell and cause the closure of the adenosine triphosphate (ATP)-dependent potassium channel (K-ATP) thereby stimulating insulin release. Their efficacy is proportional to the fasting plasma glucose (FPG) level—the higher the fasting glucose, the greater its decrease. Failure to respond to sulfonylureas may occur early due to limited beta cell availability as determined by a low C-peptide level. These reactions are primary failures. More common are the secondary failures, which accumulate over the years at a rate of 5% to 7% per year, and these patients require combination therapy with an additional agent such as metformin.

Sulfonylureas are divided into first-generation agents such as chlorpropamide and tolbutamide, and the more commonly used second-generation agents, including glimepiride, glipizide, and glyburide. Both glimepiride and one formulation of glipizide (glipizide GITS, or gastrointestinal transit system) are long acting and are taken once a day, which improves patient compliance.

The major side effect of these agents is hypoglycemia, which can be avoided by the judicious use of blood glucose monitoring and maintenance of a regular lifestyle. In addition, the use of sulfonylureas is associated with some weight gain. Recent evidence suggests that glimepiride may be

more beta-cell specific with less binding to receptors in the cardiovascular (CV) system as compared with glibenclamide (known as glyburide in the United States), and the suggestion is that glimepiride may be more appropriate for use in patients with known coronary disease (5). In addition, glimepiride produces fewer hypoglycemic attacks than glyburide, as does glipizide.

**Nonsulfonylureas.** Repaglinide and nateglinide both bind the SUR/K-ATP channel in the beta cells and stimulate rapid insulin secretion (6,7). When taken with meals, they restrict the insulin release to the period of meal digestion, thereby preventing prolonged hyperinsulinemia and reducing the risk of interprandial hypoglycemia; thus, they should be taken before every meal and generally in combination with another agent when nocturnal glycemic control is an issue. Repaglinide is capable of reducing hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) to a degree similar to that seen with the sulfonylureas. On the other hand, repaglinide seems to have a glyburide-like cardiac SUR-binding profile, whereas nateglinide apparently does not.

Repaglinide is a meglitinide analog derived from benzoic acid, and its hypoglycemic action takes effect after 45 minutes. It may be used in patients with end-stage renal disease because it is metabolized in the liver. Nateglinide is a phenylalanine derivative that is rapidly absorbed during the meal-induced early phase of insulin secretion. It is more rapid in onset, has a shorter duration of action than repaglinide, and is also metabolized in the liver.

## Biguanides

Metformin suppresses excess hepatic glucose output and, probably by reducing glucose toxicity, increases insulin sensitivity in skeletal muscle. Weight reduction is a common feature, making metformin a useful agent in obese patients with type 2 diabetes. Although uncommon, lactic acidosis is the major side effect with a frequency equal to that of glyburide-induced death from hypoglycemia. This precludes its use in patients with serum creatinine levels of  $\geq 1.4$  mg/dL and in patients with hepatic or cardiac failure. New formulations of metformin are now available, one in combination with glyburide and another as a long-acting, once-a-day tablet.

## Thiazolidinediones

Both rosiglitazone and pioglitazone enhance insulin sensitivity in muscle, liver, and adipose tissue (8,9). Their effects on insulin sensitivity make them excellent choices for use in combination therapy with sulfonylureas, metformin, or insulin. They

### KEY POINT

Initial pharmacologic therapy should include either a sulfonylurea or metformin, with insulin reserved for symptomatic patients.

also may have additional positive effects on the CV system, working through the peroxisome proliferator activated receptor gamma receptors (10). Disadvantages include a delay in initial onset of action of 8 to 10 weeks, weight gain, and water retention. The effect of water retention requires caution in prescribing these agents for patients with congestive cardiac failure or liver function abnormalities. Although weight gain is undesirable, a certain degree may be due to the generation of new fat cells that are insulin sensitive.

## $\alpha$ -Glucosidase Inhibitors

$\alpha$ -Glucosidase inhibitors slow gastrointestinal (GI) absorption of carbohydrates, which in turn reduces

postprandial blood glucose spikes. As monotherapy they are mildly effective at doses that avoid excessive flatulence, and their acceptance by patients is limited by these GI side effects.

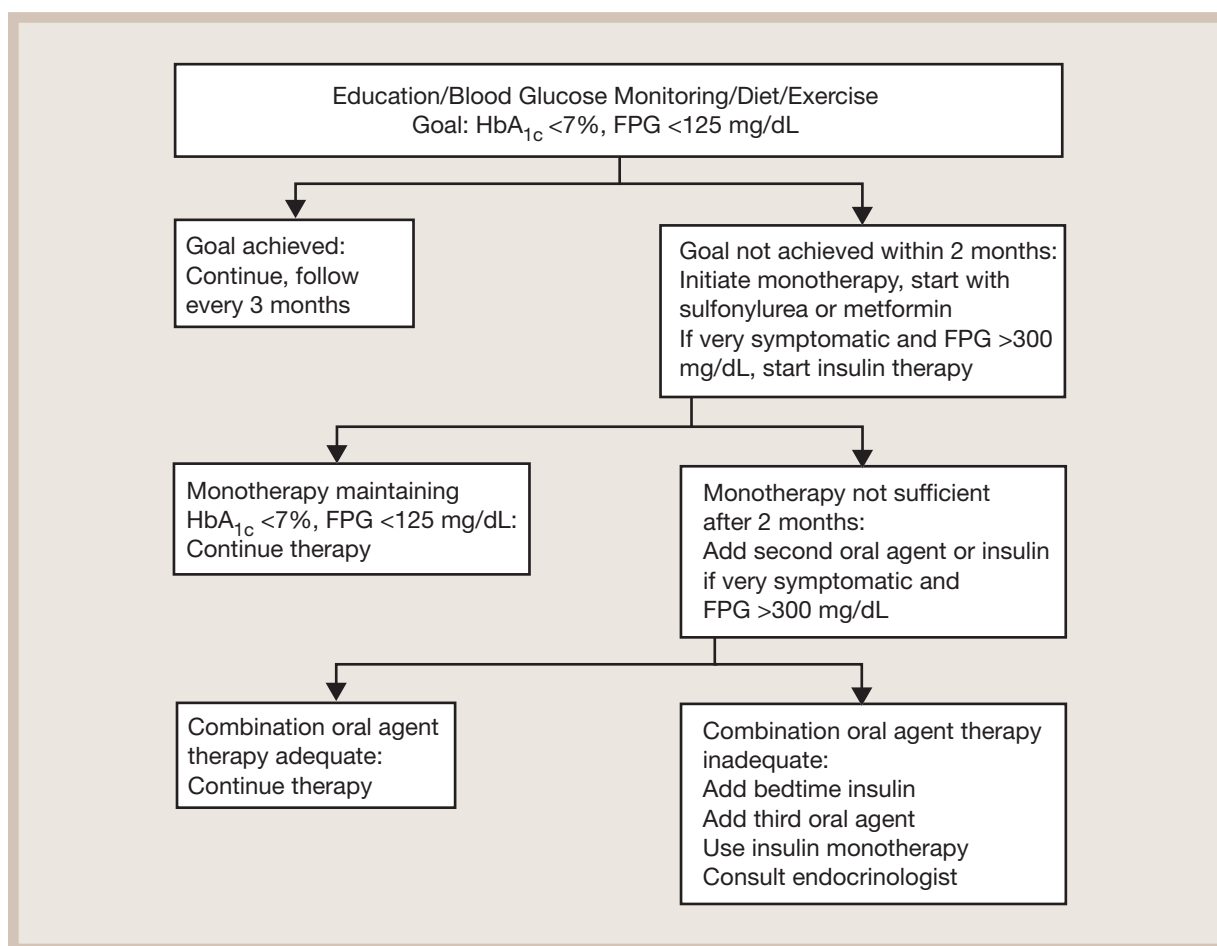
## ALGORITHMS FOR GLUCOSE CONTROL IN TYPE 2 PATIENTS

### Monotherapy

**Figure 1** outlines the generally accepted plan for treating most patients with type 2 diabetes. Because obesity and physical inactivity are risk factors for diabetes and coronary artery disease, the need for weight loss and exercise should be stressed when diabetes is initially diagnosed, and then reinforced throughout the natural history of the disease. Nutritional counseling and advice on initiating an exercise program should be a high priority (11,12).

Unfortunately, lifestyle changes are ineffective in  $>90\%$  of patients because of poor compliance, and pharmacologic intervention is generally required. Initial therapy generally includes either a sulfonylurea or metformin (the latter is often preferred for obese individuals), with insulin reserved for symptomatic patients with plasma glucose levels between 300 and 400 mg/dL, which requires immediate response to therapy. These symptoms include excessive polyuria and polydipsia, significant weight loss, and severe fatigue. Other oral agents also may be used as monotherapy. The relative efficacy of oral hypoglycemic agents is given in **Table III**. The dose of the sulfonylurea or metformin should be increased rapidly every 2 to 3 weeks until adequate glycemic control is achieved.

Only about 25% of patients will achieve adequate levels of glycemic control (FPG  $<140$  mg/dL or  $HbA_{1c} <8\%$ ) using maximum doses of sulfonylureas or metformin as monotherapy, and even fewer will reach  $HbA_{1c}$  levels of  $<7\%$ . Therefore, most patients with type 2 diabetes will require combination therapy to reach a reasonable level of glycemic control. Moreover, because type 2 diabetes is a progressive disease, even those patients achieving good initial control with a single oral agent will require in time a second or third medication. In fact, very few patients remain well controlled on monotherapy after 5 or 6 years of therapy.



**Figure 1.** Algorithm for the management of glycemia in patients with type 2 diabetes. FPG = fasting plasma glucose; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>.

### KEY POINT

**When the combination of 2 oral agents fails to maintain acceptable levels of FPG and HbA<sub>1c</sub>, there are 2 choices for improving glycemic control: one is to add a third oral agent and the other is to institute insulin therapy together with the oral agents.**

### Combination Therapy

The most commonly used combination therapy is metformin plus a sulfonylurea. The additive effect has been shown to apply to both the addition of metformin to the sulfonylurea and vice versa (13,14).

However, recent studies have demonstrated that any combination of drugs from different families of oral hypoglycemic agents is effective (Table IV).

Eventually the combination of 2 oral agents will also fail to maintain acceptable levels of FPG and HbA<sub>1c</sub> due to the progressive nature of the disease. At this stage there are 2 choices for improving glycemic control: one is to add a third oral agent and the other is to institute insulin therapy together with the oral agents. Addition of a thiazolidinedione has been shown to reduce the HbA<sub>1c</sub> in patients inadequately controlled with a sulfonylurea and metformin (15). The response to triple therapy was demonstrated by a reduction of HbA<sub>1c</sub> from an average of 9.9% to 7.8%, which was achieved in 3 months and sustained for as long as 12 months.

Although triple oral therapy is a therapeutically acceptable choice, it is probably more advisable to

TABLE III.

## RELATIVE EFFICACY OF ORAL AGENTS USED AS MONOTHERAPY

<i>Effect (Decrease In)</i>	<i>Insulin Secretagogues</i>	<i>Metformin</i>	<i>Thiazolidinediones</i>	<i>α-Glucosidase Inhibitors</i>
FPG (mg/dL)	60–70	60–70	40–50	20–30
HbA <sub>1c</sub> (%)	1.5–2.0	1.5–2.0	1.0–1.2	0.7–1.0
Triglycerides	None	Decrease	Decrease	None
HDL-C	None	Increase	Increase	None
LDL-C	None	Decrease	Increase*	None

\*Recent studies have suggested that pioglitazone may not have this effect.

FPG = fasting plasma glucose; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

TABLE IV.

## EXAMPLES OF RESPONSES TO COMBINATION THERAPY IN TYPE 2 DIABETES

<i>Regimen</i>	<i>Decrease in % HbA<sub>1c</sub></i>	<i>Decrease in FPG mg/dL</i>
Sulfonylurea and metformin	~1.7	~65
Sulfonylurea and pioglitazone	~1.2	~50
Sulfonylurea and acarbose	~1.3	~40
Repaglinide and metformin	~1.4	~40
Pioglitazone and metformin	~0.7	~40
Rosiglitazone and metformin	~0.8	~50

HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; FPG = fasting plasma glucose.

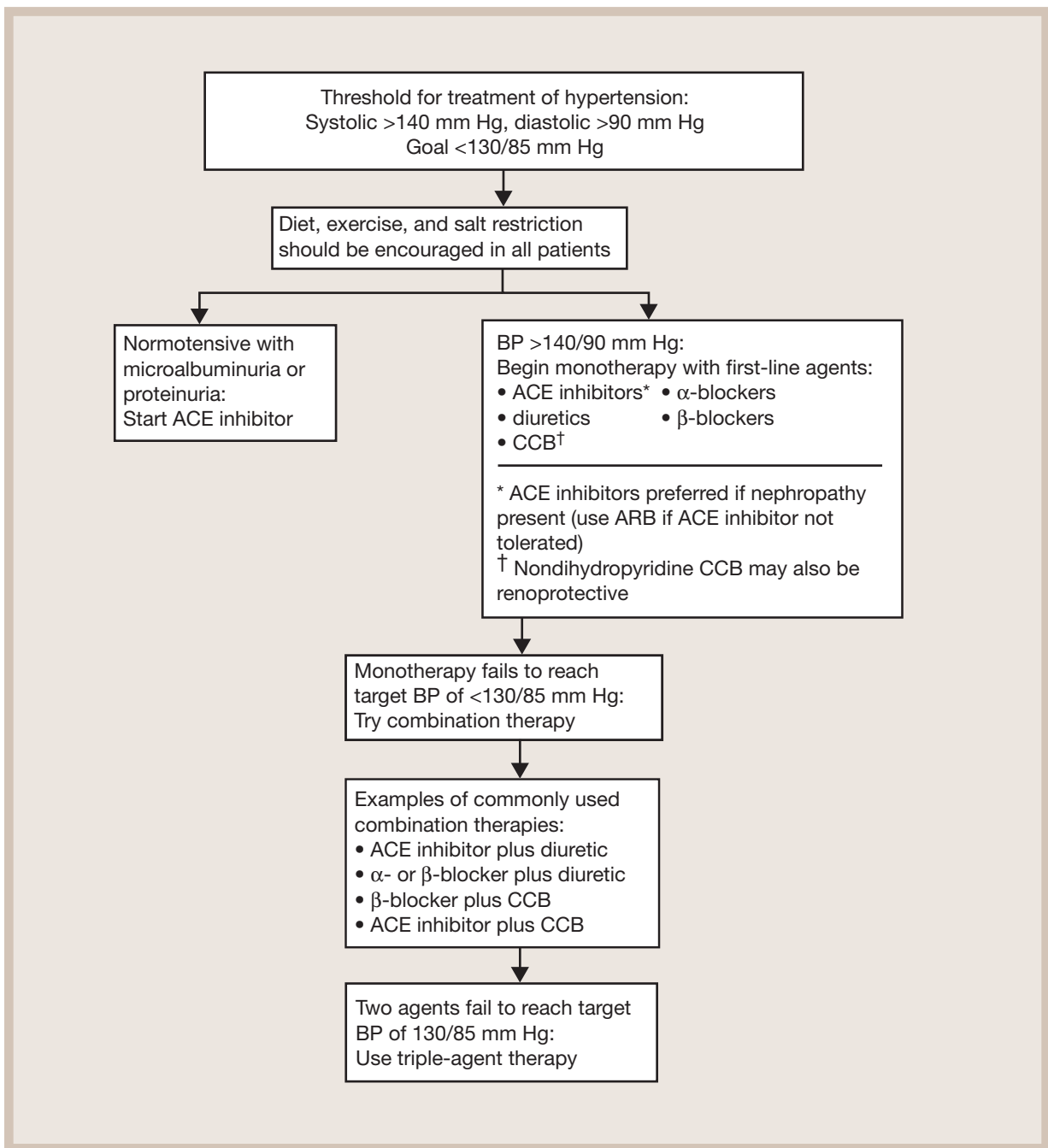
institute insulin therapy at this juncture. Because the disease is progressing, insulin therapy eventually will be necessary to control the blood glucose, and introducing a single injection daily with the oral agents is becoming a more acceptable technique (16). As glucose control improves with this combination of insulin and oral agents, 1 of the oral agents may be discontinued, leaving the patient on a daily single insulin injection and a single oral agent.

The choice of the oral agents should depend on the renal function, body weight, and status of other organ functions. Each of the major groups of oral agents—sulfonylureas, biguanides, and thiazolidinediones—has been shown to synergize with insulin injections in type 2 diabetes patients and to reduce the dose of insulin required (16). However, one of the thiazolidinedione compounds, rosiglitazone, is not approved for use with insulin.

## TREATING COMORBIDITIES

### Lipids

Most patients with type 2 diabetes will have increased plasma triglycerides, very low-density lipoprotein triglyceride concentrations, low high-density lipoprotein cholesterol (HDL-C) levels, and moderately elevated total and low-density lipoprotein cholesterol (LDL-C) plasma levels. Both total cholesterol and triglycerides are proven predictors of CV risk in diabetes, and post hoc subgroup analyses of primary prevention trials indicate that interventions to lower lipid levels reduce the rate of macrovascular disease in patients with diabetes. Diabetic patients should be treated according to National Cholesterol Education Program guidelines, with the goal being to lower LDL-C levels to <100 mg/dL and triglyceride levels to <150 mg/dL.



**Figure 2.** Algorithm for the management of hypertension in patients with type 2 diabetes. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker. Adapted with permission from the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI). Arch Intern Med. 1997;157:2413–2446; and World Health Organization—International Society of Hypertension Guidelines for the Management of Hypertension: Guidelines Subcommittee. J Hypertens. 1999;17:151–183.

Because lifestyle changes (diet and exercise) often fail to improve cholesterol levels, most patients with type 2 diabetes will require a statin to lower the LDL-C. A high dose of a statin is occa-

sionally effective in lowering triglyceride levels in these patients with combined hyperlipidemia. Fibrates, on the other hand, can effectively lower triglycerides and elevate HDL-C and should be

## KEY POINT

The approach to the treatment of dyslipidemia in type 2 diabetes should include lifestyle changes (diet and exercise); glycemic control using hypoglycemic agents to reduce triglyceride levels; and lipid-lowering agents.

used if LDL-C is not the problem. Often a statin and a fibrate may be needed together; under these circumstances close monitoring of side effects such as myositis and hepatic dysfunction is necessary. Nicotinic acid derivatives can also raise HDL-C and lower triglycerides and LDL-C, but because they worsen insulin resistance they are not generally considered first-line choices (17,18). Oral hypoglycemic agents have relatively small effects on cholesterol and triglyceride levels.

The approach to the treatment of dyslipidemia in type 2 diabetes should therefore follow these guidelines: (a) lifestyle changes (diet and exercise); (b) good glycemic control using hypoglycemic agents; and (c) lipid-lowering agents (to reduce triglyceride levels).

## Hypertension

The overwhelming evidence from recent trials has shown that reducing blood pressure between 130/80 and 130/85 mm Hg reduces CV risk by as much as 50% (17). From these studies it can be concluded that diuretics,  $\alpha$ -blockers and  $\beta$ -blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers are all acceptable means to lower blood pressure (Figure 2). Special attention should be paid to other factors that may affect the choice of an antihypertensive agent. In particular, ACE inhibitors are indicated in every diabetic patient with complications ranging from microalbuminuria to mild and severe CV alterations (19,20). Some calcium channel blockers, however, should not be used alone as they may cause increased CV disease; rather they should be used in combination with one of the other agents

mentioned earlier (Figure 2). The high frequency of impotence in the diabetic male must be considered when using  $\beta$ -blockers and thiazide diuretics, which may also adversely affect lipid profiles. In addition, these agents may worsen glycemic control to some degree.

Results of the Heart Outcomes Prevention Evaluation (HOPE) study suggest that diabetic patients who are normotensive will benefit from ACE inhibitors when other risk factors are present or even when early signs of organ involvement such as microalbuminuria are discovered (19).

The use of enteric-coated aspirin in doses of 85 to 325 mg/day is recommended for all patients >30 years of age without aspirin allergies or bleeding tendencies as primary and/or secondary prevention of vascular complications. Cessation of smoking is likewise recommended for all diabetic patients.

## SUMMARY

The ability of the primary care physician and the specialist to achieve the established goals of controlling blood glucose, lipids, and blood pressure in type 2 diabetes has been markedly enhanced by the introduction of many different agents. When lifestyle changes fail to achieve these goals, pharmacologic agents are required, often in various combinations. Given our understanding of the risks involved, we should move more rapidly to the use of combination therapies to limit the devastating complications that face the patient with type 2 diabetes.

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## Dialogue Box

### ADVISORY BOARD

**In a patient with newly diagnosed type 2 diabetes, what would prompt you to start drug therapy at the same time you initiate dietary and lifestyle interventions?**

#### LE ROITH

At the time of diagnosis, I would concurrently start an oral agent in patients symptomatic with polydipsia, polyuria, and polyphagia, as well as those with fasting glucoses >160 mg/dL or post-prandial glucoses >250 mg/dL, regardless of symptoms. In severely symptomatic patients with blood glucoses >300 to 400 mg/dL, I would start

insulin therapy immediately to reverse glucose toxicity and prescribe oral agents further on down the line.

### ADVISORY BOARD

**How much weight does a newly diagnosed type 2 diabetic need to lose before improvement in diabetic control is seen?**

#### LE ROITH

Five pounds. By just getting the patient to drop a few pounds, a dramatic though short-term improvement in blood glucose and hypertension can be achieved.



## Dialogue Box

**ADVISORY BOARD**

**What is your feeling about the so-called fad diets or the use of medications to help the diabetic patient lose weight?**

**LE ROITH**

At best such interventions are short-term solutions. The real challenge in diabetes care is to not only get the patient to lose weight but also to keep it off. For some diabetics those interventions may be of value since, by providing a period of accelerated weight loss, they help reverse glucose toxicity and may possibly help foster a desirable behavioral change. The real key to long-term weight control, however, is a long-term commitment to a healthy lifestyle that requires both a healthy diet and regular exercise.

**ADVISORY BOARD**

**Do you routinely order C-peptides in the type 2 diabetic?**

**LE ROITH**

No, I do not. The C-peptide is not really an accurate marker for beta cell functionality since we know that glucose toxicity suppresses beta cell function and thus the C-peptide will fluctuate as a result of this effect. Furthermore, interpreting any given value is difficult since we lack standardized values. It is probably best used in selective cases such as when deciding whether a type 2 patient is still a type 2 as opposed to having converted to a type 1 and requiring insulin.

**ADVISORY BOARD**

**Should one be less inclined to use a sulfonylurea in type 2 diabetes because of concerns that this agent may add to the stress on the beta cells and accelerate their exhaustion?**

**LE ROITH**

Although one might expect that insulin sensitizers would be better for the beta cells since they conceivably would allow these cells to rest, there is no evidence to suggest that the sulfonylureas cause more rapid deterioration of the beta cell. In fact, the UKPDS Study found that worsening of beta cell dysfunction in type 2 diabetics over a 10- to 12-year period was the same whether the patient was taking insulin, metformin, or a sulfonylurea. It thus appears that progressive beta cell dysfunction occurs regardless of the agent the patient is taking.

**ADVISORY BOARD**

**What is the clinical significance of the SUR on the CV system and the lesser binding seen with glimepiride among the sulfonylurea agents?**

**LE ROITH**

SURs sit in the membrane and tend to depolarize the membrane, whether the membrane is located in the pancreas or the heart. This action is good when you want to secrete insulin, but theoretically not good in the patient who's had a myocardial infarction (MI), because in that situation any change in the membrane potential may be the opposite of what the recovering heart is trying to do. With regard to the glimepiride issue, my take is that most of the sulfonylureas bind to the beta cell and have very small effects on the CV system. Of the available sulfonylureas, glimepiride may have the least effect but that's not to say the others have a lot. The UKPDS study found no increased long-term CV or MI effect in patients taking sulfonylureas; it should be noted that none of these patients were taking glimepiride. As a result, I don't believe that this particular effect of the SUR is an issue for most patients except for those having an MI, and under those circumstances I



## Dialogue Box

would not use any sulfonylurea or for that matter any of the oral diabetic agents. Instead, I would use insulin therapy. After the coronary artery process stabilizes, you can go back to a sulfonylurea agent because the heart and its membrane potential will have stabilized. Theoretically under normal circumstances, glimepiride is better; this will require additional clinical studies.

### ADVISORY BOARD

**The package insert states that metformin can be safely used provided the serum creatinine is <1.4 mg/dL in the female patient and 1.5 mg/dL in the male. Wouldn't criteria based on the creatinine clearance be more reliable when determining patient candidacy, particularly in the elderly or those with large or small muscle mass?**

### LE ROITH

The short answer to your question is that the FDA says a patient with a serum creatinine of 1.4 mg/dL and 1.5 mg/dL can safely use metformin and you shouldn't break that rule. Having said that, the creatinine clearance rate that corresponds to a serum creatinine level in a given patient, regardless of age or muscle mass, is really not an issue when deciding whether to use metformin in the ambulatory type 2 diabetic patient. Recognize that only serum creatinines were measured in the studies on which the FDA based its recommendation and that those studies undoubtedly included a wide range of patients of varying ages and muscle masses. In such studies, metformin was found to be safe in patients whose serum creatinines were found to be below the values listed in the package insert, regardless of what their creatinine clearance might have been at the time.

### ADVISORY BOARD

**What advantages do you see metformin offer-**

**ing over the other oral agents?**

### LE ROITH

Since most type 2 patients are overweight, metformin is often the first oral agent I prescribe, because it is one agent most likely to result in either a loss of weight or no gain in weight. In addition, metformin is useful in combination with a sulfonylurea, insulin, or thiazolidinedione (TZD) because it tends to dampen the weight gain typically seen with those other agents. Although metformin does offer some lipid benefits, I personally think its lipid effects are a nonfactor when compared with the effects of a statin.

### ADVISORY BOARD

**What additional positive effects on the CV system are possibly provided by the TZDs?**

### LE ROITH

There's emerging evidence that TZD use may result in a reduction of atheromatous changes within the CV system, an effect likely mediated by a favorable peroxisome proliferator activated receptor gamma effect on macrophages and oxidized LDL. It is speculated that this may be a direct effect of the TZD that is independent of its impact on insulin resistance.

### ADVISORY BOARD

**Since the TZDs reduce insulin resistance, why would they be associated with weight gain?**

### LE ROITH

For 2 reasons. First, they are associated with fluid retention and thus a lot of the weight gain is water. Second, patients treated with TZDs may actually develop new fat cells. However, unlike the fat cells associated with insulin resistance, these new cells appear to be small, insulin-responsive fat cells.



## Dialogue Box

Furthermore, it has also been speculated that TZDs may work, at least in part, by shifting fat out of the visceral fat (where they are “bad” fat cells from the standpoint of insulin responsiveness) into the peripheral subcutaneous fat where they function as “good” fat cells. In these locations, the fat cells may actually produce hormonal mediators that improve insulin sensitivity at the muscle level. Although patients may not like the look of fat deposition in areas such as the hips, from a metabolic standpoint it’s apparently good.

### ADVISORY BOARD

**Why do oral agents lose their effectiveness over time in type 2 diabetes?**

#### LE ROITH

Primarily for 2 reasons. First, the stress on the beta cells causes them to grow more dysfunctional and exhausted over time. Second, as they get older, patients tend to exercise less and to put on weight, which in turn causes their tissues to become more insulin resistant. Support for this latter factor can be seen in studies that have shown that type 2 diabetics can oftentimes regain their responsiveness to oral agents if they lose weight and exercise regularly.

### ADVISORY BOARD

**What is your perspective on the use of triple therapy?**

#### LE ROITH

I’m really not a great fan of triple therapy, which usually means you’re using a TZD with metformin and a sulfonylurea or maybe acarbose. Although triple therapy may be the only option for patients who refuse to take insulin, considering the dollar cost, the side effects, as well as the continued weight gain, I personally think that adding

a single dose of an insulin agent at bedtime, like insulin glargine, would be preferable.

### ADVISORY BOARD

**With regard to lipid management, if hypertriglyceridemia is still a problem and the patient is already taking a statin with an LDL-C at goal, do you favor increasing the statin or do you try combination therapy and add a fibrate?**

#### LE ROITH

Provided adequate glycemic control has been achieved, I would add a fibrate. Contrary to what some may say, the data really can’t support that statins are very effective at reducing triglycerides. Thus, in the patient you’re describing, if the LDLs are under 100 mg/dL and the blood sugars are reasonably well controlled, I would definitely add a fibrate if the triglyceride level is 300 mg/dL or greater.

### ADVISORY BOARD

**In that same patient, if the patient did not respond to a fibrate, would you give niacin a trial?**

#### LE ROITH

Yes, I would, since niacin is potentially going to improve both the LDL-C and the triglyceride levels. The reason it’s not recommended as a first-line drug is because we’ve always been worried about niacin being diabetogenic—in reality, its effect on glucose is really quite small. In addition, unlike the combination of a fibrate with a statin, the risk of muscle toxicity is not a big concern. Furthermore, flushing is not likely to be a problem since your diabetic patient should already be on aspirin therapy.