

CASE STUDY

A 47-Year-Old Patient With Diabetes: Insulin Resistance of a Different Kind



Presentation

A 47-year-old Hispanic female diagnosed with type 2 diabetes mellitus (T2DM) 1 year prior came for her annual physical examination. At the time of diagnosis, the patient was prescribed metformin 500 mg twice daily and advised to adopt lifestyle changes, including diet, exercise, and weight reduction. During the following month, the metformin dose was increased to 1000 mg twice daily. The patient, who maintains a well-kept appearance, was surprised when told she was overweight. As a cosmetician for an expensive line of makeup in a

large department store, she considers herself to be an attractive woman and sees no need to change her appearance. She expressed distress at the news that she has T2DM and indicated that her aunt, aged 77 years, has had diabetes for a long time. At present, her aunt is in very poor health, has end-stage renal disease, and had a leg amputated.

Physical Examination and Laboratory Values

• Height	5 ft 4 in
• Weight	172 lb (1 lb more than at diagnosis)
• Body mass index (BMI)	29.5 kg/m ²
• Waist circumference	36 in
• Blood pressure	133/78 mm Hg
• Resting heart rate	77 bpm
• Fasting plasma glucose (FPG)	220 mg/dL
• Glycosylated hemoglobin (A1C)	7.8% (0.4% lower than at diagnosis)

At the 1-year follow up, the patient admits that she has not followed the lifestyle recommendations made by her primary care clinician. She remains unconvinced that she is significantly overweight. She does not have time to go to the gym; in addition to her job as a cosmetician, she manages her household and takes care

For a quick review of type 2 diabetes therapy concepts, see page 10

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of her husband and 3 children, who are fond of the delicious meals she prepares. Changing her lifestyle would be a sacrifice that she does not see the need to make.

Clinical Decision Point

What changes in therapy should be made at this point?

- Implement intensive counseling regarding lifestyle changes
- Institute basal insulin + intensive lifestyle counseling
- Add a sulfonylurea + intensive lifestyle counseling
- Add a glitazone + intensive lifestyle counseling

Comment

No matter which pharmacologic changes are made, lifestyle counseling should be intensified for this patient. She should be led to understand that even a modest reduction in her weight (10-15 lb) may make a difference in her health and slow the progression of disease. This could be accomplished by limiting her fat intake to 25% of the total calories in a diet of ~1200 kcal per day. Patient education about the progressive nature of T2DM is important. However, <5% of patients will achieve and sustain the lifestyle changes sufficient to impact their diabetes.¹ When insulin injections are suggested, the patient is horrified at the thought. Of the choices involving an oral antidiabetic (OAD) agent, the most affordable choice recommended by the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) algorithm is a sulfonylurea.²

Decision: Add a Sulfonylurea and Intensive Lifestyle Counseling

On the advice of her healthcare provider, the patient attends several sessions with a diabetes educator at a local hospital and adds glimepiride 4 mg daily to her regimen. She starts a diet, enrolls in a dance exercise class with her husband, and loses 14 lb. Initially, she feels very good about herself and buys new clothes as a reward. Her A1C drops to 6.8%. However, she finds the strict diet hard to maintain and begins to backslide “just a little.” Her A1C creeps back up to 8.1%. She cannot believe that the minor infractions of her diet have resulted in such a large increase in her A1C. She becomes depressed and frightened that she will become like her aunt. But her fear is not enough to keep her motivated on a day-to-day basis; she strays seriously from her diet, quits exercising, and gains back the weight she lost.

Clinical Decision Point

What changes in therapy should be made at this point?

- Add exenatide, reinforce counseling
- Add a glitazone, reinforce counseling
- Add a basal insulin, reinforce counseling
- Add a prandial insulin, reinforce counseling

Comment

According to the results of several studies, it is unlikely that a combination of 3 oral agents will achieve A1C control.^{1,3,4} Exenatide is appealing from the standpoint of inducing weight loss, but in most studies it achieves A1C reduction of between 0.5% and 1.0%, less than the patient will need to achieve nationally established A1C goals. Although prandial insulin eventually may be needed, most experts believe that at A1C levels $\geq 7\%$ or more, the addition of basal insulin to the existing OADs is the best approach to helping most patients reach nationally established A1C goals.^{5,6} The ADA/EASD algorithm specifically cautions against using more than 2 OADs because of lack of effectiveness and cost, so addition of basal insulin is the most efficient and cost-effective choice at this point in the course of the disease. The addition of basal insulin is strongly supported by clinical data. The United Kingdom Prospective Diabetes Study (UKPDS) 57 demonstrated the efficacy of adding insulin in patients being treated with a sulfonylurea. Over a 6-year period, approximately 53% of patients in this study demonstrated an inadequate response to a sulfonylurea and required the addition of insulin to their treatment regimen to achieve adequate A1C levels.⁷ Patients taking a sulfonylurea plus insulin achieved lower A1C levels (6.6%) than patients taking insulin alone (7.1%) (Figure 1).

Overcoming the patient's resistance to insulin therapy is crucial. The patient is convinced that she is following the course of her aunt's disease and faces limb amputation. The patient believes that her aunt was "doing fine" until she started taking insulin. According to the patient, her aunt had diabetes "forever," with no problems until insulin was added; then her condition quickly deteriorated. It is crucial that the healthcare practitioner explain how the early introduction of insulin might have prevented this scenario.

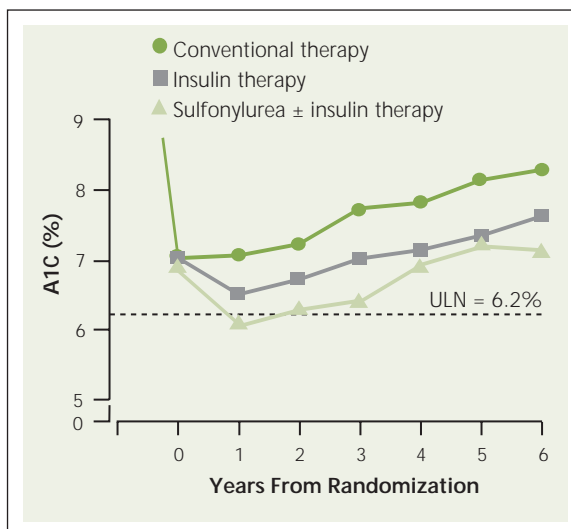


Figure 1. UKPDS: early initiation of insulin therapy improves A1C control. Median fasting A1C levels over 6 years showed that the combination of a sulfonylurea + insulin was superior to either agent alone (ULN = upper limit of A1C nondiabetic range). Wright A et al.⁷

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Table 1.
Basal Insulin Titration Algorithms

Algorithm	Function* (all start at 10 U/d of basal insulin)
2-4-6-8	Add 2, 4, 6, or 8 U of insulin glargine weekly until the mean FBG is ≤ 100 mg/dL (Riddle MC et al ⁹)
3-2-1	Add 2 U insulin glargine every 3 days until the mean FBG is ≤ 100 mg/dL (Davies M et al. <i>Diabetes Care</i> . 2005;28:1282-1288.)
3-0-3	Add 3 U insulin detemir every 3 days until the mean FBG is 80-110 mg/dL [†] (Meneghini L et al. Presented at: ADA 67th Annual Scientific Sessions. Abstract 0197-OR.)
1-1-100	Add 1 U insulin glargine each day until FBG is ≤ 100 mg/dL (Gerstein HC et al ³)

FBG = fasting blood glucose.

*See reference citations for full details of these functions and low FBG actions.

[†]See reference citation for possible twice-daily dosing information.

Decision: Add a Basal Insulin (Glargine)

Add 10 units of insulin glargine at bedtime and titrate upward using an appropriate algorithm, in this case 1-1-100 (Table 1). In this algorithm, patients are asked to increase their glargine dose by 1 extra unit every day until their FPG level is <100 mg/dL.³ Among the basal insulins, glargine provides the smoothest 24-hour response. Initially, the patient's A1C drops to 7.1%. She has titrated her glargine dose upward to 28 units but has been afraid to go higher. She is encouraged, resumes her diet, and signs up for another dance exercise class. Over time, her A1C creeps back up to 7.6%, and her morning self-monitored blood glucose readings average ~ 130 mg/dL. As her A1C value rises, she feels worse about herself and expresses doubts about the treatment regimen.

Clinical Decision Point

What changes in therapy should be made at this time?

- Reinforce counseling
- Increase basal insulin dose (glargine), reinforce counseling
- Switch to premixed 70/30 insulin, reinforce counseling
- Add a prandial insulin, reinforce counseling

Comment

Counseling is always helpful; however, the patient needs to establish an effective dose of basal insulin. The role of basal insulin is to achieve FPG of ~ 100 mg/dL without unacceptable hypoglycemia; when this target is reached, the patient is taking the correct dose of basal insulin. The patient reports no hypoglycemia, so she needs to

continue titrating her dose upward, according to the algorithm, until her morning blood sugar measurements are ≤ 100 mg/dL. Providers often believe they can establish better control by switching to pre-mixed insulins, but the ADA/EASD algorithm cautions that use of these insulins is not recommended during dose adjustment phases because it may increase the risk of hypoglycemia. Similar concerns were expressed by the investigators in the Treating to Target in Type 2 Diabetes (4-T) study.^{5,6} Even though prandial insulin may be needed, the best strategy is to “fix fasting first” and bring the FPG value to ≤ 100 mg/dL, continuing to use the 1-1-100 algorithm.

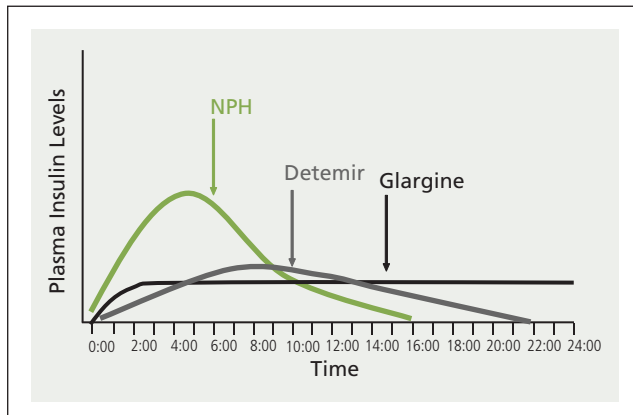


Figure 2. Idealized profiles of human insulin and basal insulin analogs. A schematic time profile of insulin concentrations. Duration of action varies among NPH (~12 hr), insulin detemir (<24 hr), and insulin glargine (≤ 24 hr). Peak actions vary as well, with insulin glargine showing a flat activity curve similar to normal physiology. Plank J et al. *Diabetes Care*. 2005;28:1107-1112; Rave K et al. *Diabetes Care*. 2005;28:1077-1082; Rosenstock J, Goldstein BJ, et al, eds. *Textbook of Type 2 Diabetes*. 2003:131-154.

Decision: Increase Basal Insulin Dose (Glargine) and Reinforce Counseling

The patient titrates upward to 47 units of glargine nightly. Her FPG readings are averaging 95 to 100 mg/dL, and she has not experienced any significant hypoglycemia. She is encouraged that she is in control of her diabetes and is pleased when she discovers her A1C is 6.6%. She is asked to check occasional blood sugar readings before and 2 hours after dinner to screen for postprandial glucose excursions outside of accepted ranges. It eventually may be beneficial to add prandial insulin to prevent postprandial glucose peaks (Figure 2), but for now, she is pleased that her A1C is within the goal range and she feels good!

Q & A: Type 2 Diabetes Therapy**What Your Colleagues Around the Country Are Asking*****PCE Atlanta*****Should diabetes treatment begin with insulin immediately, even though there are OADs that may lower A1C values?**

For patients with a starting A1C value of $\leq 9\%$, metformin is the most commonly used first-line drug for T2DM and is recommended by the ADA. If the A1C level is not controlled with metformin after ~3 months of therapy, either another OAD or basal insulin should be added as the second agent to achieve adequate control. At initial A1C values $>9\%$, insulin often is used as the starting therapeutic agent.¹

Are OADs, including metformin, appropriate to combine with insulin?

When 1 or 2 OADs are not enough to help patients achieve the ADA/AACE (American Association of Clinical Endocrinologists) goals for glycemic control, adding insulin

is appropriate. Combination therapy should be individualized, taking into account baseline A1C value, comorbidities, insulin requirements, and economics as well as patient lifestyle, convenience, and preference.⁸

Does the use of basal insulin necessitate a change in frequency of blood sugar monitoring?

It's a good idea to introduce home monitoring as soon as the patient starts taking metformin. Once basal insulin is introduced, it is important to add education about insulin administration through a comprehensive diabetes class or other source. At that time, morning blood glucose levels should be monitored daily to guide basal insulin dose titration, and prandial and postprandial levels should

be monitored periodically until A1C is controlled (usually within ~3 months). Once A1C is under control, monitoring can be performed less frequently.

What is the best algorithm for patients to increase their basal insulin dosage?

There is no specific algorithm that is best for all patients. The goal is to guide patients toward their blood glucose goals in a reasonable amount of time. In the Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment (INSIGHT) study, Gerstein and colleagues³ recommend a simple algorithm: with the 1-1-100 algorithm, patients are sent home with basal insulin (glargine) and asked to increase the dose by 1 extra unit every (1) day, until their FPG value is ≤ 100 mg/dL (5.6 mmol/L).

When is the best time to administer basal insulin, in the morning or at bedtime?

The pharmacokinetics and pharmacodynamics of basal insulins vary, so the time of administration must take into account the type of basal insulin being used and possibly the dose. For the long-acting analogue basal insulins (glargine and detemir), generally there is no right or wrong time for patients to administer the dose, as long as it is taken at approximately the same time every day. Whatever time best fits the patient's lifestyle is appropriate.

When should mealtime insulin be added?

Basal insulin should be used in combination with OADs to achieve a morning blood glucose reading of 100 mg/dL and adequate A1C control. However, if the A1C level creeps up over time despite adequate fasting blood sugar control, the patient's mealtime blood glucose control should be addressed and mealtime insulin added if necessary.

If mealtime insulin is added, should the basal insulin dose be decreased to avoid hypoglycemia?

Morning blood glucose levels should be monitored when mealtime insulin is added. If the morning value starts dropping, then basal insulin should be cut back appropriately. Often, a few units of basal insulin are shifted over to the mealtime dose for better balance of coverage.

Because most patients with T2DM need insulin therapy at some point, why not be more aggressive and consider basal insulin as second-line therapy after exercise?

The ADA and EASD, in a consensus statement, recommend the use of metformin with exercise in the initial treatment of patients with T2DM. If blood glucose is not controlled, then insulin should be added. Studies have shown the best A1C control is achieved with a regimen of insulin plus OADs.⁷

What are the pros and cons of using neutral protamine Hagedorn (NPH) insulin?

Although patients with T2DM taking NPH insulin can achieve good FPG and A1C control, glucose-lowering activity with NPH insulin peaks between 4 and 8 hours after injection,⁹ forcing patients to eat defensively, suffer from hypoglycemia, or be treated with a suboptimal dose. In addition, the duration of action of NPH insulin is only ~12 hours, requiring multiple doses for full-day basal coverage.

Under what conditions are insulin pumps the best option?

Although insulin pumps provide excellent blood glucose control, they are used more commonly in patients with type 1 diabetes because they are more likely to require intensive insulin treatment regimens. Pump users must self-monitor with multiple blood glucose

Q & A: Type 2 Diabetes Therapy

determinations daily and administer multiple doses to receive full benefit from the pump. The patient must be willing to wear a pump and usually needs insurance to pay for it. Not all insurance companies will cover the cost of insulin pumps for patients with normal C-peptide levels.

How long should lifestyle interventions be tried before initiating oral therapy for T2DM?

According to the ADA/EASD consensus algorithm, metformin should be started immediately. Although diet and exercise help reduce blood glucose levels,¹⁰ only a small percentage of patients diagnosed with T2DM will initiate and follow the appropriate lifestyle modifications needed to successfully manage T2DM.

Should a patient's metformin dose be maximized before adding a second drug?

Yes. Few OADs differ much in activity at lower and higher doses; however, it is worthwhile to titrate metformin to the maximum dose before adding insulin or another OAD.

When is the use of an incretin mimetic (eg, exenatide) for T2DM appropriate?

Exenatide is reasonable to use when the patient approaches the A1C goal but has weight management concerns. However, since exenatide often is associated with nausea and its ability to lower A1C is limited ($\leq 1\%$), it is not appropriate for the majority of patients with T2DM. It should also be kept in mind that although exenatide is an injectable, it not a substitute for insulin.

Do the benefits of glitazones outweigh the risks?

It appears that all glitazones are not the same, and there is conflicting evidence about the ability of glitazones to raise or lower cardiovascular (CV) disease risk. A widely published meta-analysis indicated there may be

evidence of possible increased CV disease risk with rosiglitazone.¹¹ There also is evidence of CV disease protection with pioglitazone from the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study. Unlike rosiglitazone, pioglitazone is associated with lowering plasma triglyceride levels and elevating levels of high-density lipoprotein cholesterol (HDL-C). Because T2DM is a CV disease risk equivalent, clarity about this drug class is imperative and should be forthcoming. Until more is known, care should be taken with rosiglitazone with respect to possible CV event risks.

What about kidney function and metformin?

Generally, metformin should not be used when the patient's serum creatinine value is >1.5 mg/dL.

With the epidemic of obesity, even in children and adolescents, should metformin be used in adolescents who have T2DM?

It would be prudent to stress diet, exercise, and weight management more aggressively in adolescents than in adults with T2DM and to move more slowly to the use of medication in this population. If an adolescent patient is unable or unwilling to control blood glucose levels with lifestyle modifications, then OAD therapy should be initiated with metformin.

Should individuals with prediabetes be treated with OADs?

The Diabetes Prevention Program (DPP) study showed that diet, exercise, and weight management may prevent the development of T2DM in ~60% of patients with prediabetes.¹⁰ However, only a small percentage of patients will make sufficient lifestyle modifications to prevent T2DM. Results from the DPP indicate that metformin plus lifestyle modifications may prevent diabetes.

Additionally, the ADA suggests medical therapy for prediabetes.¹⁰ In those patients who are not successful in maintaining lifestyle changes, use of metformin is reasonable.

Should an angiotensin-converting enzyme (ACE) inhibitor be the first antihypertensive agent used in patients with T2DM to protect the kidneys?

According to the ADA standard of care, an ACE inhibitor or an angiotensin receptor blocker is indicated for kidney protection in those with T2DM and should be used as a first-line agent.

In patients with T2DM and dyslipidemia, should blood glucose and lipids be controlled sequentially or concomitantly?

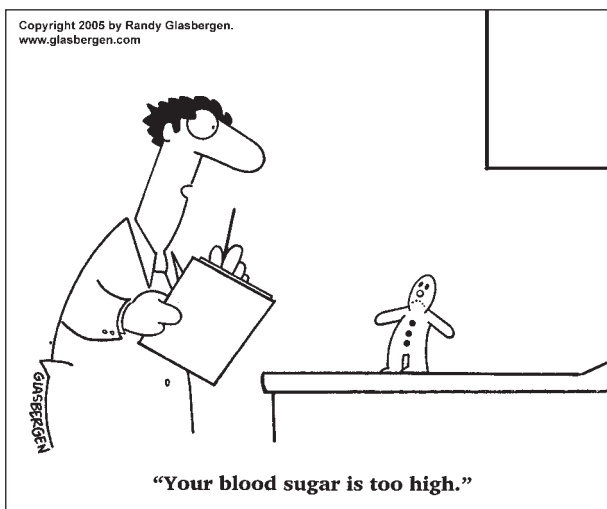
All CV disease risk factors (eg, hypertension, dyslipidemia, tobacco smoking) should be treated simultaneously in patients with T2DM.

Are elevated triglyceride levels combined with low HDL-C levels considered a marker for prediabetes?

Yes, this combination is often associated with insulin resistance.¹² Patients with this combination should be counseled to adopt lifestyle modifications, FPG levels should be monitored, and lipid parameters treated aggressively to attain nationally established goals.

When should patients with T2DM be referred to an endocrinologist?

Endocrinologists see only a small percentage (~10%-15%) of patients with T2DM. This is due to many factors, including a scarcity of endocrinologists and the fact that T2DM therapy should be well within the core competence of most primary care providers (PCPs). Usually, lifestyle instruction, institution of 1 or 2 OADs, and initiation and titration of basal insulin can be handled by the PCP. More and more PCPs are comfortable adding mealtime insulin. When the patient cannot achieve national goals for A1C reduction despite starting and advancing these appropriate therapies in a timely fashion, then referral to an endocrinologist is appropriate.



Optimizing Type 2 Diabetes Therapy: Earlier Insulin Use

WHAT is the extent of our nation's diabetes epidemic?

Diabetes mellitus is highly prevalent, affecting ~10% of the adult population. It is the sixth leading cause of death in the United States, associated with twice the risk of death seen in persons of the same age without diabetes.¹³

The majority of these patients have T2DM, which may progress without recognizable symptoms in its early stages. Unfortunately, by the time patients are aware of symptoms, irreversible damage has likely occurred. The prevalence of T2DM is steeply on the rise. Since 1990, its prevalence has increased by 61%, and an estimated 14.6 million persons in the United States have a condition labeled prediabetes, characterized by blood glucose levels above the normal range but below the values that define frank diabetes (Table 2). Unlike type 1 diabetes, T2DM is characterized by an often lengthy, progressive decline in the function of insulin-secreting pancreatic beta cells.

In addition to the 14.6 million individuals diagnosed with T2DM in 2005, approximately 6.2 million persons with



T2DM are undiagnosed. Prevalence increases steeply with age, from approximately 10% in persons aged 40 to 59 years to ~21% in persons ≥ 60 years of age. The prevalence is higher among Native Americans, non-Hispanic black persons, and Hispanic individuals compared with non-Hispanic white persons.¹³

WHY is early detection important?

Complications associated with T2DM may start years before glucose levels indicate frank diabetes. It is estimated that approximately 20% of patients with T2DM have retinopathy at diagnosis, and microvascular and CV complications can precede diagnosis by ≥ 5 years.¹⁴ Peripheral arterial disease is twice as common in patients with diabetes^{6,7} (see *Peripheral Arterial Disease: Twice as Common in Patients With Diabetes*, pages 12-14).

Table 2.
Diagnostic Criteria for Diabetes and Prediabetes

Disorder	Blood Glucose Criteria
Diabetes	Casual plasma glucose ≥ 200 mg/dL; or FPG ≥ 126 mg/dL; or 2-hr plasma glucose ≥ 200 mg/dL during OGTT
IFG	FPG 100-125 mg/dL
IGT	2-hr plasma glucose 140-199 mg/dL during OGTT

OGTT = oral glucose tolerance test; IFG = impaired fasting glucose; IGT = impaired glucose tolerance. ADA.²

There is a large and disturbing health outcomes disparity between persons with and without T2DM. Adults with T2DM are 3.2 times more likely to report a history of coronary heart disease, 2.9 times more likely to report a history of stroke, and 1.9 times more likely to report other heart condition(s) than those without diabetes. In adults aged 35 to 64 years, these disparities are even more extreme: for coronary heart disease, the ratio is 5.1 to 1; for stroke, 4.9 to 1; and for other heart condition(s), 2.4 to 1.¹⁵ Approximately 65% of persons with T2DM die of heart disease or stroke.¹³

WHAT are the treatment goals for T2DM?

Several organizations offer recommended treatment goals, with the principal parameter being blood levels of A1C; however, other CV disease risk-factor target goals also are recommended (Table 3).

Optimal target A1C levels vary among guidelines. The ADA goal, based on supportive evidence from well-conducted cohort studies, is an A1C level <7.0%. There

Table 3.
Treatment Goals for T2DM

Organization	Parameter	Target
ADA/EASD AACE	A1C	<7.0% ≤6.5%
ADA	FPG	90-130 mg/dL
ADA	Postprandial PG	<180 mg/dL
ADA	LDL-C	<100 mg/dL
ADA	TG	<150 mg/dL
ADA	HDL-C	>40 mg/dL
ADA	BP	<130/80 mm Hg

Nathan DM et al¹; ADA²; AACE. *Endocr Pract*. 2007;13:1-68.

is evidence, however, that A1C reductions <7% may reduce complications. Therefore, the ADA recommends that individual patients try to achieve an A1C level as close to normal (<6.0%) as possible without hypoglycemia.²

In addition to diet and exercise, there are a number of therapeutic interventions for T2DM available (Table 4). Importantly, no oral medication by itself can reduce A1C by more than 1.5%, and most agents do not achieve even that level of success.

(continued on page 15)

Table 4.
T2DM Interventions: Mechanisms of Action

Intervention	Mechanism of Action	Expected A1C Decrease (%)
Diet and exercise	Decrease insulin resistance	1.0-2.0
Metformin	Decreases hepatic glucose output	1.5
Sulfonylureas, meglitinides, exenatide	Increase insulin secretion	0.5-1.5
α-Glucosidase inhibitors	Delay GI absorption of carbohydrates	0.5-0.8
Sitagliptin	Prevents glucagon-like peptide (GLP)-1 breakdown	0.6-1.0
Thiazolidinediones (TZDs)	Increase insulin sensitivity	0.5-1.4
Insulin	Increases insulin levels	1.5-2.5

ADA. Available at: <http://www.diabetes.org>. Ahren B. *Diabetes Care*. 2007; 30:1344-1350. Nathan DM et al¹; Nathan DM.¹⁷

Peripheral Arterial Disease: Twice as Common in Patients With Diabetes Warning Signs, Diagnosis, and Treatment

WHY should clinicians check for peripheral arterial disease in their patients with type 2 diabetes mellitus?

It is well established that chronic hyperglycemia as measured by A1C is a risk factor for type 2 diabetes mellitus (T2DM)-associated microvascular disease.^{1,2} Recent studies have established a link to macrovascular disease as well, including coronary heart disease, stroke, and peripheral arterial disease (PAD).³⁻⁵ More than twice as common among patients with diabetes,^{6,7} PAD is a strong predictor of subsequent cardiovascular (CV) morbidity and mortality.⁸⁻¹⁰ Improving glycemic control in persons with T2DM may substantially reduce the risk of PAD.¹¹

WHO else is at risk and should be evaluated for PAD?

Patients known to have CV disease should be evaluated for PAD. The principal noncardiac risk factors for PAD are smoking¹² and T2DM.¹¹ Hypertension and elevated total

cholesterol also increase the risk of PAD.¹³ In addition, there are the nonmodifiable risk factors of race (non-Hispanic blacks are at higher risk), age (>40 years), and in younger age groups (<40 years), male gender.¹⁴

HOW can clinicians detect PAD?

A number of physical examination findings suggest the presence of PAD.¹⁵ The examination should be performed with the patient's pants and shoes removed. The limbs are compared for differences in skin tone and color, nail growth, or hair loss, and the presence of arterial bruits, tissue ulceration, or diminished pulses.¹⁶ The ankle-brachial index (ABI) is a key tool for detecting PAD. This test is based on segmental blood pressure (BP) measurement. With arterial narrowing, systolic BP measurements drop progressively as the distance from the site of the blockage increases.¹⁷ The ABI is the ratio of the BP recorded in the leg to the higher of the BPs recorded in the left and

TABLE 1.
PAD: Aggressive Risk Factor Modification

Smoking Cessation Goal: Abstinence	↓ Severity of claudication (probably) Slows progression to critical leg ischemia ↓ MI risk, vascular deaths	Pharmacotherapy (NRT, nortriptyline, clonidine, bupropion) + counseling
Exercise Goal: As frequently and as long as possible	↑ Peak walking time ↑ Peak oxygen consumption ↑ Pain-free walking time ↑ Quality of life ↑ Routine daily activities	Therapeutic exercise training
Treat Hyperlipidemia Goal: LDL-C <100 mg/dL	↓ Serum cholesterol ↑ Endothelial function ↓ Disease progression Modifies other atherosclerotic risks	Statins Niacins
Treat Hypertension Goal: <140/90 mm Hg <130/80 mm Hg (diabetes or renal insufficiency)	Data support aggressive treatment; impact on PAD outcomes unclear	ACE inhibitors β-Blockers can be used
Control Diabetes Goal: A1C <7% or as close to normal (<6%) as possible	↓ CV disease and MI rates; trend for PAD outcomes ↓ Limb infection, amputation ↓ Microvascular complication risk	Diet, exercise, pharmacotherapy

NRT = nicotine replacement therapy.

Hiatt WR¹²; Norgren L et al¹⁴; Gey DC et al¹⁵; Stewart KJ et al. Exercise training for claudication. *N Engl J Med.* 2002;347:1941-1951.

right arms. In a healthy person, systolic BP in the leg is approximately the same as in the upper arm¹⁷; when the ankle pressure is compared with the higher of the right or left brachial pressures, the index should be ≥ 1 . An ABI score ≤ 0.9 is suggestive of PAD, with progressively lower ABI scores indicating more severe occlusion.¹⁷ The American Diabetes Association recommends the following steps for measuring the ABI^{13,18}:

- Gather equipment (pressure cuff and handheld Doppler probe)
- Have patient rest in supine position for 5 minutes
- Measure BP in both arms; use higher value as reference
- Position cuff above ankle
- Measure pressure in dorsalis pedis artery
- Measure pressure in posterior tibial artery
- Repeat process in opposite leg

WHAT are the goals of therapy and current treatment options?

The goals of therapy for PAD are to relieve the symptoms that occur on exertion and improve patients' ability to walk and quality of life. If patients have pain after a physical activity they regularly take part in, drug treatment may be warranted. For patients with severe PAD who present with critical leg ischemia, the goals are the same as for patients with claudication, with some important additions (ie, to relieve the pain patients feel at rest, heal ischemic ulcers, and prevent further deterioration that could lead to amputation).¹²

Patients with PAD are candidates for secondary prevention strategies, including aggressive risk factor modification (Table 1) (the first step in any treatment plan for PAD) and antiplatelet therapy (Table 2).

Aspirin 81 to 325 mg/d is the first choice for antiplatelet therapy.¹⁹ Used in combination with dipyridamole, aspirin increases pain-free walking

distance and resting limb blood flow and improves patients' coagulation profile and ABI.¹⁹ Clopidogrel prevents adenosine diphosphate (ADP) activation of platelets by selectively and irreversibly inhibiting ADP binding to platelets. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, clopidogrel was compared with aspirin for prevention of a composite outcome of ischemic stroke, MI, or vascular death.²⁰ The study enrolled 19,185 patients who were followed for a mean of 1.91 years.²¹ Compared with aspirin, treatment with clopidogrel resulted in an 8.7% reduction in risk of the composite outcome.²¹

Antiplatelet therapy may increase the risk of bleeding. In the CAPRIE study, however, no increase in bleeding was seen with clopidogrel compared with aspirin.²² Among patients treated with aspirin, there was significantly ($P < .05$) more gastrointestinal (GI) hemorrhage, including severe GI bleeding, and a higher number of intracranial hemorrhagic events. Rash and diarrhea occurred more often with clopidogrel than with aspirin; GI discomfort occurred more often with aspirin.²¹ The incidence of serious adverse events was judged by investigators to be low in both groups.²¹

The current recommendation is that all symptomatic PAD patients be treated with antiplatelet therapy using aspirin or clopidogrel to reduce the risk of CV disease and death.¹⁴

TABLE 2.
PAD: Antiplatelet and Vasodilator Therapy

ASA 81-325 mg/d PO	Recommended by ACCP; not FDA-approved
Clopidogrel 75 mg/d PO	Fewer side effects than ASA in CAPRIE trial; significantly less TTP risk than ticlopidine
Pentoxifylline 1.2 g/d PO	Some effect on walking ability; insufficient data to support widespread use
Cilostazol 100 mg BID PO	Correct dosage critical; avoid in patients with heart failure; reduce dose in patients taking CCBs; GI side effects

ACCP = American College of Chest Physicians; ASA = aspirin; CCB = calcium channel blocker; GI = gastrointestinal; TTP = thrombotic thrombocytopenic purpura. Adapted from Gey DC et al.¹⁵

Peripheral Arterial Disease: Twice as Common in Patients With Diabetes Warning Signs, Diagnosis, and Treatment

References

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
3. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141:421-431.
4. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.
5. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes: the Atherosclerosis Risk in Communities study. *Arch Intern Med*. 2005;165:1910-1916.
6. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110:738-743.
7. Gregg EW, Sorlie P, Paulose-Ram R, et al. Prevalence of lower-extremity disease in the U.S. adult population ≥ 40 years of age with and without diabetes: 1999-2000 National Health and Nutrition Examination Survey. *Diabetes Care*. 2004;27:1591-1597.
8. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PWF. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. *Arch Intern Med*. 2003;163:1939-1942.
9. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*. 1999;19:538-545.
10. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381-386.
11. Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care*. 2006;29:877-882.
12. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;344:1608-1621.
13. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study Collaborative Research Group. *Circulation*. 1993;88:837-845.
14. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, on behalf of the TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;45(Suppl S):S5A-S67A.
15. Gey DC, Lesho EP, Manngold J. Management of peripheral arterial disease. *Am Fam Physician*. 2004;69:525-532.
16. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985;71:510-515.
17. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation*. 1996;94:3026-3049.
18. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg*. 2000;31:S1-S296.
19. Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and noninvasive test results in patients referred for peripheral arterial disease testing. *Vasc Med*. 1996;1:65-71.
20. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
21. Kanjwal MK, Cooper C, Bashir R. Peripheral arterial disease—the silent killer. *JK Practitioner*. 2004;11:225-232.
22. Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb Company and Sanofi Aventis; 2007.

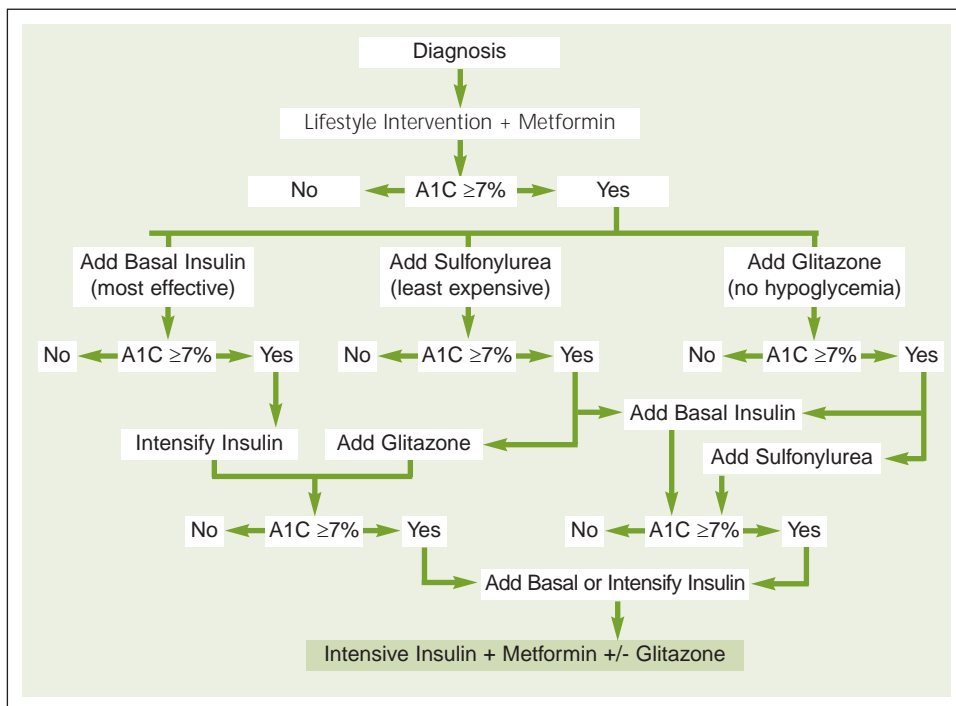


Figure 3. ADA/EASD consensus algorithm for T2DM. A1C levels should be checked every 3 months until $<7\%$ and then at least every 6 months thereafter. Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred, based on effectiveness and expense. Nathan DM et al.¹ Copyright © 2006 American Diabetes Association. From *Diabetes Care*, Vol. 29, 2006; 1963-1972. Reprinted with permission from The American Diabetes Association.

Recently, a consensus statement was developed by the ADA and the EASD that recommends lifestyle modification plus metformin use as the first step in the management of hyperglycemia in T2DM, based on the important realization that lifestyle modification fails for most patients in the first year (Figure 3). Progression to the second (or subsequent) therapeutic agent is based on A1C levels measured at timely intervals (usually ~3 months), with a level $\geq 7.0\%$ as the “call to action to initiate or change therapy with the goal of achieving an A1C level as close to the nondiabetic range as possible, or, at a minimum, decreasing the A1C to $<7\%$.”¹

HOW does intensive treatment affect patient prognosis?

The large, long-term UKPDS brought to light the importance of intensive treatment in the T2DM population. The UKPDS compared conventional T2DM treatment with intensive treatment (ie, a sulfonylurea or insulin). A1C values dropped steeply in the initial 5-year period, with the intensive therapy group achieving mean values of 6.6% compared with 7.4% for the conventional group. These values rose over time in both groups, reaching 8.1% and 8.7%, respectively, by the end of the third 5-year period. Patients receiving intensive treatment had a 12% lower relative risk of sustaining

Optimizing Type 2 Diabetes Therapy: Earlier Insulin Use

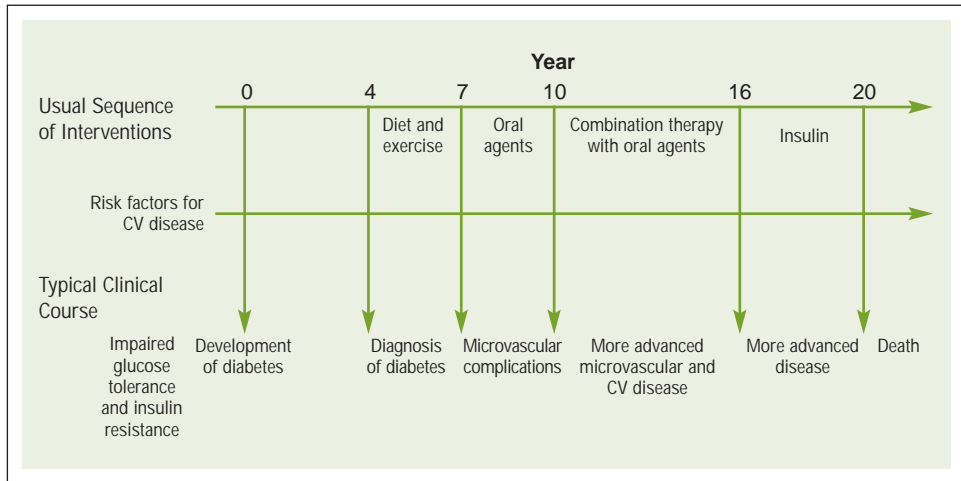


Figure 4. Typical clinical course of T2DM. Development of T2DM precedes diagnosis by 4-7 years on average. Approximately 20% of T2DM patients have microvascular or neurologic complications at the time of diagnosis. Nathan DM.¹⁷ Copyright © 2002 Massachusetts Medical Society. All rights reserved.

any diabetes-related end point, a 25% lower risk of microvascular complications, and a nonsignificant 16% lower risk of sustaining a myocardial infarction.¹⁶

However, despite improved outcomes in the intensive treatment group, A1C levels in this group increased to 8.1% as beta-cell function inexorably declined during the 15-year study period, a level above which ADA/EASD guidelines clearly recommend intensifying treatment.

WHEN is insulin best incorporated into treatment?

The usual sequence of T2DM treatment is based on an assumption that initially there is some residual beta-cell function, and therefore some endogenous insulin production, so the disease can initially be managed with OADs. These drugs act by increasing the sensitivity of insulin receptors, decreasing hepatic glucose secretion, preventing glucose absorption, or increasing insulin secretion (Table 4). However, usefulness diminishes

and ultimately disappears as beta-cell function declines. Moreover, during the interval between prediabetic changes and the eventual initiation of insulin therapy (which may be ≥ 15 years), advanced microvascular and CV complications are likely to occur, suggesting that usual treatment for T2DM does not prevent the development of serious and ultimately fatal complications (Figure 4).¹⁷

In contrast with OADs, the effectiveness of exogenous insulin in no way depends on beta-cell function. The only limit to lowering A1C levels with the administration of insulin is the risk of hypoglycemia, which is infrequent in persons with T2DM.¹⁸ The ADA/EASD treatment algorithm suggests clinicians consider initiating insulin treatment whenever the patient's A1C rises above 7.0% despite initial oral therapy and lifestyle changes. Because disease progression varies by patient, many factors must be considered in the tailoring of a treatment strategy, including the patient's overall health and CV disease risk. The ADA notes that for

individual patients presenting with weight loss, more severe symptoms, and blood glucose values >250 to 300 mg/dL, early initiation of insulin therapy is a safer approach.²

WHICH type of insulin should be used first?

The initial insulin therapy for T2DM recommended by the ADA is basal (background) insulin, which has a longer duration of action than rapid-acting prandial (bolus) insulin and provides coverage for basal insulin needs throughout the day. There are 3 principal basal insulins: NPH, with a duration of action of ~ 12 hours, and a peak of action of 4 to 6 hours after subcutaneous administration; insulin detemir, whose duration of action is slightly <24 hours and peaks slightly about halfway through that period; and insulin glargine, which has a duration of action of ≥ 24 hours and a flat activity curve similar to that in normal human physiology. In

addition, there are premixed insulin preparations designed to mimic the physiologic insulin response by combining basal insulin with bolus or prandial insulins that control plasma glucose increases following meals. The complex action peaks of premixed insulin make titration more cumbersome and for that reason, it is not recommended during dose adjustment phases.¹ Basal insulin doses are adjusted daily to weekly, following an established algorithm (Table 1, page 4), until the desired FPG levels are reached or progress is impeded by hypoglycemia; during this phase, premixed insulins are not advisable. Adapting the insulin regimen to the patient takes time and requires careful monitoring.

WHAT are the barriers to initiating insulin therapy?

Patients may prefer OADs to insulin administration because of a fear of injections. Insulin delivery methods now in use,

Clinical Pearls

- Recommend FPG testing in patients with risk factors for T2DM, even when the primary complaint is unrelated. Risk factors for T2DM include ≤ 45 years of age, BMI ≥ 25 kg/m², habitual inactivity, family history of T2DM, high-risk ethnicity, and previous FPG values in the impaired glucose tolerance and/or insulin resistance range²
- Emphasize to patients that the goal of treatment is to prevent end-stage organ damage and CV disease. Educate patients about T2DM pathophysiology, especially the typical decline in beta-cell function and insulin response with this disease, with the implication that patients should expect to intensify treatment^{13-15,17}
- Explain to patients that insulin use is a normal part of diabetes treatment as beta-cell function declines: it is not a last-ditch intervention when OADs fail and the patient experiences significant complications^{1,17}
- Closely monitor all patients with T2DM for markers such as elevated blood pressure and dyslipidemia. Guidelines such as those published by the Seventh Joint National Committee (JNC 7) and Third Adult Treatment Panel (ATP III) set more stringent blood pressure and lipid targets for patients with diabetes^{1,2}
- Continual reinforcement is essential for diabetes management. Providers should be aware of the high rate of nonadherence to diet and exercise recommendations¹

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including pen devices, may allay those fears: the needles are tiny, silicone-coated, and inflict no pain. Patients also may believe that progressing to insulin treatment means they have failed all previous attempts to control their disease, and they are now in the terminal stages. Good patient education can correct that misperception, presenting early initiation of insulin as the best way to prevent complications due to T2DM.

Clinicians, too, may be reluctant to start insulin treatment, persisting in the point of

view that insulin is the treatment of last resort rather than an early intervention to prevent complications. There may be concerns about weight gain, hypoglycemia, and other adverse effects, including a possible contribution to atherogenesis. Misconceptions about insulin use should not dissuade clinicians from offering this treatment option to their patients. Weight gain can be controlled, hypoglycemia is rare in T2DM (and usually mild when present), and insulin is not atherogenic.

Track 1

Ask the Expert Audio Interview on Type 2 Diabetes

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Interviewed by: Mary D. Knudtson, DNSc, NP
Clinical Professor
Department of Family Medicine
University of California, Irvine
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Please take this brief quiz before listening to the accompanying audio CD.

1. What criteria should be used to diagnose T2DM?
 a. A1C >7%
 b. FPG \geq 126 mg/dL
 c. Blood sugar taken 2 hours after a meal \geq 200 mg/dL
 d. b or c
2. Which is a potential marker for pre-diabetes?
 a. Elevated triglyceride levels
 b. Large waist circumference
 c. Low HDL-C levels
 d. All of the above
3. What is the importance of the A1C measurement?
 a. Diagnosis of diabetes
 b. Diagnosis of IGT
 c. Standard marker of success in treatment of patients with diabetes
 d. Management of blood sugar changes throughout the day
4. Which insulin is *not* the best option for initiating insulin treatment?
 a. Insulin detemir
 b. Insulin glargine
 c. NPH insulin

(Answers to these questions appear on page 106)

References

1. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes [published correction appears in *Diabetes Care*. 2006;49:2816-2818]. *Diabetes Care*. 2006;29:1963-1972.
2. American Diabetes Association. Standards of medical care in diabetes — 2007. *Diabetes Care*. 2007;30(suppl 1):S4-S41.
3. Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas: the Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. *Diabet Med*. 2006;23:736-742.
4. Willey CJ, Andrade SE, Cohen J, Fuller JC, Gurwitz JH. Polypharmacy with oral antidiabetic agents: an indicator of poor glycemic control. *Am J Manag Care*. 2006;12:435-440.
5. McMahon GT, Dluhy RG. Intention to treat—initiating insulin and the 4-T study. *N Engl J Med*. 2007;357:1759-1761.
6. Holman RR, Thorne KI, Farmer AJ, et al, for the 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357:1716-1730.
7. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR, for the U.K. Prospective Diabetes Study Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U. K. Prospective Diabetes Study (UKPDS 57) [published correction appears in *Diabetes Care*. 2002;25:1268]. *Diabetes Care*. 2002;25:330-336.
8. Kuritzky L. Addition of basal insulin to oral antidiabetic agents: a goal-directed approach to type 2 diabetes therapy. *MedGenMed*. 2006;8:34. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?&artinstid=1868361>. Accessed December 19, 2007.
9. Riddle MC, Rosenstock J, Gerich J, for the Insulin Glargine 4002 Study Investigators. The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26:3080-3086.
10. Knowler WC, Barrett-Connor E, Fowler SE, for the Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
11. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published correction appears in *N Engl J Med*. 2007;357:100]. *N Engl J Med*. 2007;356:2457-2471.
12. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report. *Circulation*. 2002;106:3143-3421.
13. National Diabetes Information Clearinghouse, a service of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. National diabetes statistics. Available at: <http://diabetes.niddk.nih.gov/dm/pubs/statistics/>. Accessed January 2, 2008.
14. Ramlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes: implications for clinical practice. *PrimCare*. 1999;26:771-789.
15. Centers for Disease Control and Prevention (CDC). Self-reported heart disease and

Diabetes: References

- stroke among adults with and without diabetes — United States, 1999-2001. *MMWR Morb Mortal Wkly Rep.* 2003;52:1065-1070.
16. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): UK Prospective Diabetes Study (UKPDS) Group [published correction appears in *Lancet.* 1999;354:602]. *Lancet.* 1998;352:837-853.
 17. Nathan DM. Clinical practice: initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med.* 2002;347:1342-1349.
 18. UK Hypoglycaemia Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia.* 2007;50:1140-1147.