

Clinically effective approaches to meeting the American Diabetes Association's guidelines: Glycated hemoglobin and lipids

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Diabetes can be a devastating illness. In the United States, it is the leading cause of blindness in individuals between the ages of 20 and 74 years.¹ It is also the leading cause of patients undergoing dialysis, with almost 50% of those starting dialysis having kidney failure secondary to diabetic nephropathy.² Diabetic peripheral neuropathy leading to foot ulcers is the underlying cause of non-traumatic lower extremity amputations in patients with diabetes.³ More than half of lower extremity amputations occur in diabetic individuals,⁴ although only approximately 7% of the population has recognized diabetes.⁵ Myocardial infarctions (MIs) are twice as common in diabetic men and 4 to 5 times more common in diabetic women than in nondiabetic individuals.⁶ Strokes are twice as common⁷ and peripheral arterial disease is 2.5 times more common⁸ in patients with diabetes compared with disease-free subjects. Approximately 90% of diabetic patients have type 2 diabetes and two thirds die from MIs and strokes.⁵

Although these numbers are startling, these complications are avoidable. The microvascular complications of diabetes could be markedly reduced, if not eliminated, if near euglycemia

could be maintained. Progression of early kidney disease to late-stage nephropathy can be forestalled by appropriate (nonglycemic) therapy. Although macrovascular disease is not entirely preventable, its effects could be sharply curtailed with appropriate lipid and blood pressure management, smoking cessation, and aspirin therapy. The American Diabetes Association (ADA) has promulgated standards of care regarding glycated hemoglobin (HbA_{1c}), low-density lipoprotein (LDL) cholesterol, and blood pressure (Table); if these objectives were met, the complications caused by diabetes would be greatly attenuated.⁹ Currently, only 2% to 10% of diabetic patients meet all 3 of the ADA's HbA_{1c}, LDL cholesterol, and blood pressure goals.¹⁰⁻¹³ The first of this 2-part series will focus on HbA_{1c} and lipid goals. Pages 14 and 15 provide at-a-glance glycemia and dyslipidemia protocols.

ADA HbA_{1c} goals

There have been 5 studies in over 2000 type 1¹⁴⁻¹⁶ and type 2^{17,18} diabetic patients that showed virtually no development or progression of retinopathy and nephropathy over 4 to 9 years if mean HbA_{1c} levels of less than 7.0% were maintained. Figure 1 shows this

relationship in type 1 diabetic patients enrolled in DCCT (Diabetes Control and Complications Trial). In 2 studies,^{14,17} interventions that lowered glycemia resulted in considerably fewer microvascular complications, proving a causative relationship between near-euglycemia and improved outcomes.

There is much less evidence that lowering glycemia will have a beneficial effect on macrovascular disease, at least in the near- to mid-term. Although there is an association between glycemia and cardiovascular disease (CVD), this relationship extends into the mid-normal range.¹⁹ For instance, in men between the ages of 40 and 74 years, there was an approximately 2.5-fold increased risk of an MI in those with HbA_{1c} levels between 5.0% and 5.4% compared with those who had HbA_{1c} levels lower than 5.0% over 4 years.²⁰ In another study involving nondiabetic adults, there was an approximately 2-fold increased risk of CVD events in individuals with HbA_{1c} levels in the upper quintile (>5.2%) compared with those in the lowest quintile (<4.6%).²¹ In earlier studies²² and in a meta-analysis of these studies,²³ no benefit on CVD was seen by lowering glycemia in patients with type 2 diabetes.

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Three larger recent studies also failed to find a beneficial effect with glucose control on CVD events. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, 10,251 patients (median baseline HbA_{1c} level of 8.1%), 35% of whom have had a previous CVD event, were randomized to receive intensive (goal HbA_{1c} level <6.0%) or usual care (goal HbA_{1c} level of 7.0%-7.9%).²⁴ The study was stopped after 3.5 years because of a significantly higher mortality rate in the intensively treated group compared with the control group, with achieved median HbA_{1c} levels of 6.4% and 7.5%, respectively.

In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study, 11,140 patients (mean HbA_{1c} level of 7.5%) with a history of major macrovascular or microvascular disease or at least 1 other risk factor (besides diabetes) for vascular disease were randomized to receive intensive glucose control (goal HbA_{1c} ≤6.5%) or standard glucose control (targeted HbA_{1c} according to local guidelines).²⁵ At the end of the study, which had a median duration of 5 years, there was no difference in major macrovascular events, including nonfatal MI, nonfatal stroke, and death from CVD, between the intensively treated patients (achieved mean HbA_{1c} of 6.5%) and those treated using standard protocols (achieved mean HbA_{1c} of 7.3%). There was a significant reduction in the development of nephropathy in the intensively treated group, which has also been found in numerous other studies examining microvascular complications.

In the VADT (Veterans Affairs Diabetes Trial),²⁶ 1791 veterans with a mean baseline HbA_{1c} of 9.4% were randomized to receive intensive or standard treatment. Of these patients, 40% had a prior CVD event. At the end of the study, which had a median

Table. Treatment guidelines recommended by the American Diabetes Association.

Guideline	Frequency	Goal or protocol
HbA _{1c}	Every 6 months if goal attained; every 3 months if greater	<7.0%
LDL cholesterol	Annually (or more often, if needed)	<100 mg/dL
Triglycerides	Annually (or more often, if needed)	<150 mg/dL ^a
Renal profile	Annually (or more often, if needed)	<i>Dipstick for proteinuria</i> ≥1+ ^b : ACE inhibitor unless contraindicated Negative or trace: evaluation for microalbuminuria <i>Microalbuminuria</i> Positive ^c and confirmed: ACE inhibitor unless contraindicated
Blood pressure	Every routine diabetes visit	<130/80 mm Hg
Eye examination	Annually (or less frequent if exam is normal)	Yearly dilated fundoscopic examination starting at diagnosis in type 2 diabetic patients and within 3-5 years of diagnosis in type 1 diabetic patients; less frequent examinations (every 2-3 years) may be considered in the setting of a normal eye exam. Examination by retinal photographs (with or without pupil dilation) that are read by experienced optometrists also can be done.
Foot examination	Annually for comprehensive foot exam; visual inspection at every routine diabetes visit, especially for those with neuropathy	Comprehensive foot examination should include assessment of protective sensation (with a Semmes-Weinstein 5.07 [10g] monofilament), foot structure and biomechanics, vascular status, and skin integrity.
Aspirin therapy	Daily	75-162 mg daily, unless contraindicated
Smoking cessation	Initial visit (subsequent visits, if needed)	Smokers should be encouraged to quit smoking.

ACE indicates angiotensin-converting enzyme; HbA_{1c} = glycated hemoglobin; LDL = low-density lipoprotein.

^aSee text for discussion on treating triglycerides.

^bWith infection and menstrual bleeding ruled out.

^cEither albumin:creatinine ratio >30 µg/mg or albumin concentration >20 µg/L.

duration of 5.6 years, there was no difference in major CVD events, including death, MI, stroke, heart failure, amputation secondary to ischemia, and intervention for coronary or peripheral arterial disease in the intensive treatment (achieved HbA_{1c} of 6.9%) and standard treatment (achieved HbA_{1c} of 8.4%) groups. As in the ADVANCE study, there was a significant decrease

in the progression of albumin excretion in the intensively treated group.

Recent evidence suggests, however, that lowering glycemia may have a long-term benefit on both microvascular and macrovascular disease. In the UKPDS (United Kingdom Prospective Diabetes Study),²⁷ 5102 patients with newly diagnosed type 2 diabetes were randomized to receive either intensive

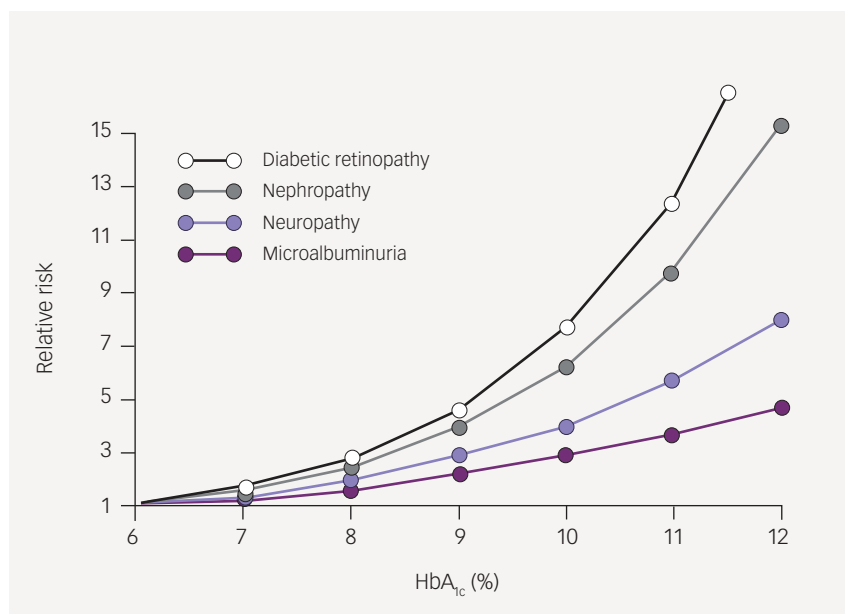


Figure 1. Relationship between progression of microvascular complications and mean HbA_{1c} levels during DCCT (Diabetes Control and Complications Trial). Although the individual complications cannot be differentiated, the lack of progression for all subjects with HbA_{1c} levels <7.0% is obvious. Figure reprinted with permission from Skyler JS. Diabetic complications: the importance of glucose control. *Endocrinol Metab Clin North Am.* 1996;25(2):243-254.

glucose control (n = 2729) with sulfonylureas or insulin or to standard glucose control (n = 1138), initially with diet. Baseline HbA_{1c} levels were 7.1% in both groups and remained 7.0% in the intensive group, but increased to 7.9% in the standard group when the study ended after a median of 10 years. During the active-treatment phase of UKPDS, there were significant reductions in diabetes-related end points and microvascular disease in the intensively treated group. There was also a 16% reduction in MI in the intensively treated group, which just missed statistical significance ($P < .052$). After the trial ended, patients were followed clinically for 5 years and by questionnaires for an additional 5 years. Between group differences in HbA_{1c} levels were lost within the first years after the study ended and were approximately 7.8% at the last measurement 5 years later.²⁸ By 10 years, the significant differences in any diabetes-related end point and microvascular disease persisted, and since more CVD

events occurred over time, the 15% reduction in MIs and the 13% reduction in death from any cause became statistically significant in patients originally assigned to intensive treatment versus standard treatment. This is termed a legacy effect and is consistent with long-term results of DCCT.

In DCCT, 1441 type 1 diabetic patients (baseline HbA_{1c} level of 9.1%) were randomized to receive either intensive or standard treatment and followed for a mean of 6.5 years.²⁹ At the end of the study, there was a 1.7% difference in HbA_{1c} levels between the intensive-treatment and standard-treatment groups, with levels of 7.4% versus 9.1%, respectively. The patients were then followed for a mean of 17 more years.³⁰ As in the UKPDS, between group differences were quickly lost, with the original intensive- and standard-treatment groups maintaining mean HbA_{1c} levels of 7.9% and 7.8%, respectively. Although there was no difference in macrovascular disease (CVD is unusual in young type 1 dia-

betic patients) during the intervention study, there was a 57% reduction in the first occurrence of nonfatal MI, stroke, or CVD death at the end of the observational follow-up period.³⁰ There was also a legacy effect on the subsequent progression of retinopathy and nephropathy in the intensively treated group.^{31,32} Those who progressed had significantly more accumulation of advanced glycated end products than those who did not progress.³² These compounds, which last in tissues for many years and have been implicated in causing both the microvascular and macrovascular complications of diabetes, may account for the legacy effect of earlier good control.

ADA lipid goals

Lowering LDL cholesterol has a causative effect on reducing cardiac events in the general population.³³ Lipid-lowering drugs are equally effective in reducing the relative risk of coronary disease in people with and without diabetes (ie, the percent reduction is the same).³⁴ The reduction of absolute risk, however, is 3-fold greater in diabetic patients.³⁴ This warrants a brief explanation of relative and absolute risks. As an example, if one considers HbA_{1c} levels, every 10 percentage point decrease in these levels is associated with an approximately 40% decrease in the risk of sustained progression of diabetic retinopathy.¹⁴ Estimating from the curves in **Figure 2**, the absolute risk of sustained progression at a mean HbA_{1c} level of 10% is approximately 8 patients per 100 patient-years, whereas the absolute risk for patients with a mean HbA_{1c} level of 8% is only slightly over 2 patients per 100 patient-years. A 40% relative risk reduction seen with a 10 percentage point fall in HbA_{1c} levels from 10% to 9% results in about 5 patients developing sustained progression per 100 patient-years, a decrease of 3 patients. A 40% relative risk reduction

seen with a 10 percentage point fall in HbA_{1c} levels from 8% to 7.2% results in about 1 less patient per 100 patient-years showing sustained progression. Therefore, a 1% decrease in HbA_{1c} levels from 10% benefits 3 times as many patients as a 1% decrease from 8%.

Figure 2 summarizes the effects of LDL cholesterol lowering on coronary artery disease reduction observed in a number of primary and secondary prevention studies in type 2 diabetic patients. It also highlights the relationship between baseline absolute risk on the X-axis and absolute risk reduction on the Y-axis. Although the relative risk reduction was similar across all studies, as shown by the equivalent slopes of the lines for primary and secondary prevention, higher absolute baseline rates in the secondary prevention trials were associated with greater reductions in absolute risk.

Relative risk reduction is similar across all baseline LDL cholesterol levels, equally beneficial in older and younger diabetic patients, and in men and women.^{35,36} There is an approximately 20% relative risk reduction for a 40-mg/dL decrease in LDL cholesterol levels.^{33,37} Based on these findings, it is not surprising that cardiac events were 25% lower in diabetic patients receiving 80 mg of atorvastatin compared with 10 mg.³⁸ Treatment of approximately 30 type 2 diabetic patients with a statin will prevent 1 major cardiac event over 4 years.^{39,40} Routine monitoring of liver function tests and creatinine and creatine phosphokinase (CPK) levels are unnecessary, except in specific circumstances (eg, if patients have pertinent symptoms, baseline abnormalities of liver function tests, a myopathy already present at baseline, or are taking drugs that interact with statins and increase the risk for adverse events).⁴¹ The use of statins has been shown to be cost-effective.^{42,43}

Based on these data, the ADA⁹ recommends that all type 2 diabetic

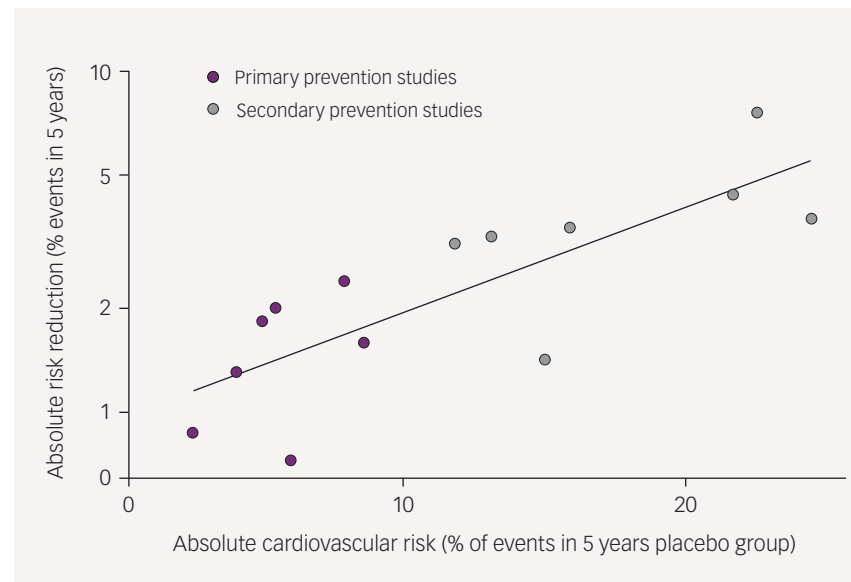


Figure 2. Relationship between absolute cardiovascular risk (X-axis) and absolute risk (Y-axis) reduction in primary and secondary prevention trials for cardiovascular disease. Primary prevention: MEGA, FIELD, HHS, ASCOT, AFCAPS, LRC, WOSCOPS. Secondary prevention: BIP, HPS, CARE, LIPID, VA-HIT, PROSPER, 4S. Figure reprinted with permission from Sirtori CR, Calabresi L. Japan: Are statins still good for everybody? *Lancet*. 2006;368(9542):1135-1136.

patients over the age of 40 years should receive a statin regardless of their baseline LDL cholesterol levels (see dyslipidemia protocol on page 15). The goal for patients without clinical evidence of CVD is less than 100 mg/dL. For those with clinical evidence of CVD, the goal is to lower levels to below 70 mg/dL. Only 60% of type 2 diabetic patients with CVD and 45% of those without CVD currently meet the LDL cholesterol goal of less than 100 mg/dL.⁴⁴

What about triglyceride concentrations? Very high triglyceride levels (>1000 mg/dL) can cause pancreatitis. Patients presenting with values above 1000 mg/dL, therefore, should initially be treated with a fibrate. Because all diabetic patients over 40 years of age will also be taking a statin, the fibrate should be a fenofibrate, not gemfibrozil. The combination of a fibrate and a statin increases the risk of side effects; however, a fenofibrate is less likely to result in side effects because it does not affect the pharmacokinetics of statins,

unlike gemfibrozil.

Very few patients have high enough triglyceride levels to require initial fibrate treatment; however, many patients will have elevated triglyceride levels and depressed high-density lipoprotein (HDL) cholesterol levels. It is not clear whether the risk is mainly due to high triglyceride levels or to low HDL cholesterol levels. Fenofibrate treatment of type 2 diabetic patients who were not taking a statin⁴⁵ had much less of an effect on CVD than statins.^{33,34} The National Cholesterol Education Program (NCEP)⁴⁶ and the ADA⁹ suggest that once the LDL cholesterol goal is reached, non-HDL cholesterol (total cholesterol minus HDL cholesterol) should be calculated in patients whose triglyceride levels are greater than 200 mg/dL. Triglycerides are carried on many different lipoproteins, and non-HDL cholesterol levels reflect the more atherogenic ones. The goal for non-HDL cholesterol is to achieve a level less than 130 mg/dL.

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If the non-HDL cholesterol goal is not achieved after the LDL cholesterol goal is met, submaximal doses of the statin should be progressively increased until both goals are met. If the non-HDL cholesterol goal is still not achieved by a maximal dose of a statin other than atorvastatin or rosuvastatin, the patient should be switched to the maximal dose of one of these statins. Patients in whom non-HDL cholesterol goals remain unmet may also be prescribed ezetimibe. If the non-HDL cholesterol level is 130 mg/dL or higher despite the combination of a maximal dose of atorvastatin or rosuvastatin plus ezetimibe, adding a fibrate is the next step; however,

because of the greater chance for side effects with the combination of a statin plus a fibrate, addition of a fibrate should be avoided unless the non-HDL cholesterol value exceeds 160 mg/dL, and then fenofibrate should be used rather than gemfibrozil. This protocol is based on a meta-analysis of 4 large lipid studies⁴⁷ that showed that CVD mortality in patients with and without diabetes only increased with non-HDL cholesterol values of 160 mg/dL or higher. Furthermore, when this combination of pharmacotherapy is used, CPK levels and transaminases should be measured every time that lipids are measured.

Conclusions

Diabetes can be a debilitating illness, especially when near euglycemia is not achieved and other CVD risk factors remain uncontrolled, including lipid levels. The ADA has issued guidelines to enable physicians to optimize the care of patients with diabetes. Part 2 of this series will examine the ADA's stance on blood pressure management, smoking cessation, aspirin therapy, as well as important components of the physical examinations, including eye and foot examinations. •

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Glycemia Protocol

Treatment plan

1. Principles of treatment:

a) Type 1 diabetes: Patients require insulin.

b) Type 2 diabetes: This is a progressive disease. The initial treatment is medical nutrition therapy, increased physical activity, and metformin. Over time, combinations of different classes of oral drugs are required, and in many cases, insulin eventually becomes necessary.

2. Goals:

a) Fasting plasma glucose (FPG) concentration <130 mg/dL.

b) Glycated hemoglobin (HbA_{1c}) level <7.0% (in a DCCT [Diabetes Control and Complications Trial] standardized assay with normal range of 4%-6%). This is the most important goal.

3. Progression of treatment in type 2 diabetic patients:

a) Diet and exercise should be used initially and continuously in conjunction with all therapies.

b) Monotherapy: All type 2 diabetic patients should be started on metformin, 500 mg twice daily with meals (unless contraindicated). Measure FPG concentration in 2 weeks. If value is >130 mg/dL, increase by 1 step (500 mg). Continue to increase by 1 step every 2 weeks until either:

(1) FPG ≤130 mg/dL (then wait 3 months and measure HbA_{1c} level),

or

(2) Maximal (tolerated) dose is reached and FPG is still >130 mg/dL. In that case, start a sulfonylurea (glipizide, 10 mg; glyburide, 5 mg; or glimepiride, 2 mg). Glimepiride is preferred because it is taken only once daily, even at higher doses. Also, glyburide causes more hypoglycemia than glipizide or glimepiride.

c) Dual therapy: Continue to measure the FPG concentration every 2 weeks. Increase the sulfonylurea by 1 step (10 mg for glipizide, 5 mg for glyburide, or 2 mg for glimepiride) until either:

(1) FPG is ≤130 mg/dL then wait 3 months and measure HbA_{1c} level),

or

(2) Maximal dose of the sulfonylurea is reached (glipizide, 20 mg twice daily; glyburide, 10 mg twice daily; or glimepiride, 8 mg once daily) and FPG is still >130 mg/dL. Measure HbA_{1c} level and if >7.0%, add maximal dose of pioglitazone (45 mg).

(3) Equivalent doses (mg) of the 3 sulfonylureas are as follows:

Glimepiride	Glipizide	Glyburide
2	10	5
4	20	10
6	30	15
8*	40*	20*

*maximal dose

d) Triple therapy:

(1) Since it takes at least 8 weeks and can take up to 12 to 16 weeks before a maximal effect of a glitazone is seen, a decision on its effectiveness is made 4 months after starting pioglitazone.

(2) If HbA_{1c} >7.5% 4 months later, start bedtime insulin and discontinue pioglitazone.

e) Bedtime insulin:

(1) Start obese patients with 16 units of Neutral Protamine Hagedorn (NPH) insulin and lean patients with 10 units of NPH insulin at bedtime.

(2) Gradually increase insulin dose until self-monitored blood glucose values before breakfast are between 90 and 130 mg/dL more than 50% of the time.

(3) Wait 3 months and measure HbA_{1c} level.

(4) If HbA_{1c} >7.5%, switch to mixed/split regimen.

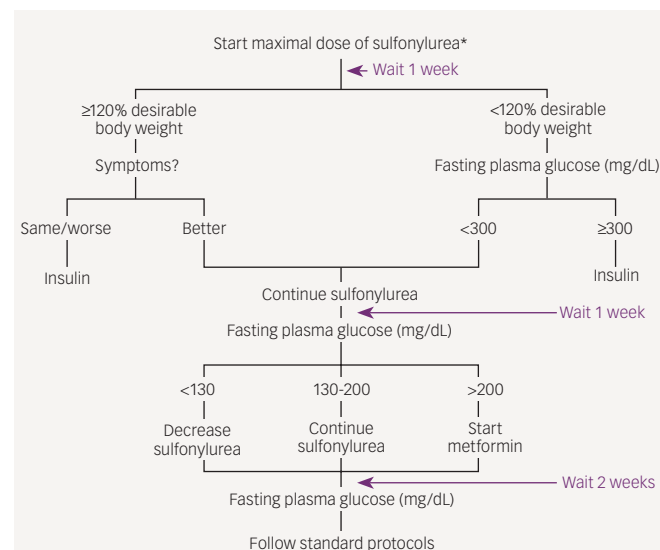
f) Two or more daily injections of insulin: Adjust each component of the insulin regimen until ≥50% of appropriate preprandial self-monitored blood glucose values are within target range (70-130 mg/dL).

g) Relationship of each component of the insulin regimen and self-monitored blood glucose test best reflecting its effect:

Insulin	Time injected	Test reflecting insulin action
Regular, Lispro, Aspart, Glulisine	Before a meal	Both following meal, before which insulin is injected, and before next meal or bedtime snack (if insulin is taken before supper)
NPH	Before breakfast	Before supper
NPH	Before supper or bedtime	Before breakfast
Glargine, Detemir	Before breakfast or before supper or half dose each time	Before breakfast

4. Treatment of markedly symptomatic newly diagnosed type 2 diabetic patients:

a) These patients have marked polyuria, polydipsia, and often blurring of vision and weight loss. Glucose concentrations frequently exceed 400 mg/dL. Almost all of these patients can be successfully treated with high doses of sulfonylurea(s).



*Start with half-max dose if patient is >65 years old and increase to max dose at 1 week if no response.

Glycemia and dyslipidemia protocols were based on treatment algorithms used by nurses in a minority population. Report was published in *Am J Manag Care*. 2006;12(4):226-232.

Dyslipidemia Protocol

Treatment plan (direct low-density lipoprotein [LDL] cholesterol measurements not available)

1. Measure baseline lipid panel. (Hepatic transaminases should be measured every time lipids are.)
2. All diabetic patients ≥ 40 years old should be taking a statin regardless of baseline LDL cholesterol concentration.
3. Goal level of LDL cholesterol is < 100 mg/dL or < 70 mg/dL if patient has overt cardiovascular disease (CVD).
4. Start a statin in *all* patients ≥ 40 years old and in those < 40 years whose LDL cholesterol remains above goal levels after lifestyle modification or in the setting of multiple CVD risk factors.
5. In patients not at goal level, measure LDL cholesterol 1 month after starting a statin, and measure LDL cholesterol at monthly intervals and increase dose of drug until goal level is achieved.
6. Drug titration:
 - a) Start simvastatin (Zocor), 10 mg at bedtime, and double each month as follows until goal is achieved: 10 mg \rightarrow 20 mg \rightarrow 40 mg \rightarrow 80 mg. If goal is still not achieved, switch to 80-mg atorvastatin (Lipitor). If goal is still not met 1 month later, add 10 mg of ezetimibe (Zetia). If goal is still not met 1 month later, consult specialist, if uncomfortable intensifying therapy further.
 - or**
 - b) Start Vytorin (combination of ezetimibe [Zetia] plus simvastatin) 10/10 mg at bedtime and increase each month as follows until goal is achieved: 10/10 mg \rightarrow 10/20 mg \rightarrow 10/40 mg \rightarrow 80 mg atorvastatin plus 10-mg ezetimibe; if goal is not met 1 month later, consult specialist, if uncomfortable intensifying therapy further.
7. If initial triglyceride (TG) concentration is ≥ 1000 mg/dL, also start fenofibrate (Tricor) at 130 mg once daily and measure TG concentration in 1 month.
 - a) If TG concentration remains ≥ 1000 mg/dL, continue fenofibrate and consult specialist, if uncomfortable intensifying therapy further.
 - b) If TG concentration < 1000 mg/dL, discontinue fenofibrate but restart if subsequent TG concentrations increase to ≥ 1000 mg/dL, and consult specialist, if uncomfortable intensifying therapy further.
8. When LDL cholesterol is at goal, if TG concentration is 200 to 999 mg/dL, calculate the non-HDL cholesterol (non-HDL cholesterol = total cholesterol – HDL cholesterol); if this value > 130 mg/dL (> 100 mg/dL in patients with overt CVD), keep increasing the statin dose (see 6a or 6b) monthly until appropriate goal is reached.
9. If the patient reaches 80-mg atorvastatin plus 10-mg ezetimibe and the non-HDL cholesterol value is 130 to 159 mg/dL, simply follow the patient. If the non-HDL cholesterol value is ≥ 160 mg/dL, and the patient is not taking fenofibrate, add 130-mg fenofibrate.
10. When LDL cholesterol (and non-HDL cholesterol, if TG concentrations are 200-999 mg/dL) is/are at goal, measure lipids every 4 months during the subsequent year and every 6 months thereafter. Intensify treatment as described above if lipids increase above goal levels.

Treatment plan (direct LDL cholesterol measurements not available)

1. Measure baseline lipid panel. (Hepatic transaminases should be measured every time lipids are.)
2. All diabetic patients ≥ 40 years old should be taking a statin regardless of baseline LDL cholesterol concentration.
3. Goal level of LDL cholesterol is < 100 mg/dL or < 70 mg/dL if patient has overt CVD.
4. Start a statin in all patients ≥ 40 years old and in those < 40 years whose LDL cholesterol remains above goal levels after lifestyle modification or in the setting of multiple CVD risk factors.
5. If initial TG concentration < 400 mg/dL and patient is not at LDL cholesterol goal, measure LDL cholesterol 1 month after starting a statin and continue to measure at monthly intervals, increasing drug dose until goal level is achieved.
6. Drug titration:
 - a) Start simvastatin (Zocor), 10 mg at bedtime and double each month as follows until goal is achieved: 10 mg \rightarrow 20 mg \rightarrow 40 mg \rightarrow 80 mg. If goal is still not achieved, switch to 80-mg atorvastatin (Lipitor). If goal is still not met 1 month later, add 10 mg of ezetimibe (Zetia). If goal is still not met 1 month later, consult specialist, if uncomfortable intensifying therapy further.
 - or**
 - b) Start Vytorin (combination of ezetimibe [Zetia] plus simvastatin) 10/10 mg at bedtime and increase each month as follows until goal is achieved; 10/10 mg \rightarrow 10/20 mg \rightarrow 10/40 mg \rightarrow 80 mg atorvastatin plus 10-mg ezetimibe; if goal not met 1 month later, consult specialist, if uncomfortable intensifying therapy further.
7. When LDL cholesterol is at goal level, if TG concentration is 200 to 399 mg/dL, calculate the non-HDL cholesterol (non-HDL cholesterol = total cholesterol – HDL cholesterol); if this value is > 130 mg/dL (> 100 mg/dL in patients with overt CVD), keep increasing the statin dose (see 6a or 6b) monthly until this goal is reached.
8. If the patient reaches 80-mg atorvastatin plus 10-mg ezetimibe and the non-HDL cholesterol value is 130 to 159 mg/dL, simply follow the patient. If the non-HDL cholesterol value is ≥ 160 mg/dL, and the patient is not taking fenofibrate, add 130-mg fenofibrate.
9. If initial TG concentration is 400 to 999 mg/dL, calculate the non-HDL cholesterol. If this value is > 130 mg/dL (> 100 mg/dL in patients with overt CVD), keep increasing the statin dose (see 6a or 6b) monthly until the appropriate goal is reached.
10. If initial TG concentration is ≥ 1000 mg/dL, also start fenofibrate (Tricor) at 130 mg once daily along with 10-mg simvastatin at bedtime and measure TG concentration in 1 month.
 - a) If TG concentration remains ≥ 1000 mg/dL, continue fenofibrate and consult specialist, if uncomfortable intensifying therapy further.
 - b) If TG concentration is < 1000 mg/dL, discontinue fenofibrate but restart it if subsequent TG concentrations increase to ≥ 1000 mg/dL and consult specialist, if uncomfortable intensifying therapy further.
11. When LDL cholesterol (and/or non-HDL cholesterol if TG concentrations are 200-999 mg/dL) is/are at goal, measure lipids every 4 months during the subsequent year and every 6 months thereafter. Intensify treatment as described above if lipids increase above goal levels.