

# Contributions of Fasting and Postprandial Plasma Glucose Levels to Glycosylated Hemoglobin and Diabetes Mellitus–Related Complications: Treating Hyperglycemia with Insulin

George E. Dailey, MD

Senior Consultant, Division of Diabetes and Endocrinology; Head, Diabetes Research, Scripps Clinic; Clinical Professor of Medicine, University of California at San Diego, La Jolla, California

## ABSTRACT

**Background:** Glycosylated hemoglobin (A1C) is a good indicator of a patient's mean plasma glucose level over the previous 90 to 120 days. It can assist in determining whether fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels are under control in a patient with diabetes mellitus. Self-monitoring of blood glucose levels is essential to distinguish the contributions of FPG and/or PPG when a change occurs in the A1C level.

**Objectives:** The goal of this article was to define A1C and address the contributions of FPG and PPG levels to overall A1C. Elevated A1C levels correlate with an increased risk of cardiovascular disease and other complications, which are also reviewed here. Available therapies and therapeutic strategies are discussed, including the use of insulin when oral therapy alone has not maintained glycemic control.

**Methods:** English-language articles (1990–2006) were searched on the PubMed database using the following terms: *insulin, type 2 diabetes, early insulin use, A1C, and hemoglobin A1C*.

**Results:** Several studies are presented here which demonstrate that blood glucose levels can dramatically improve when insulin is added to the existing regimen of oral therapy or when administered alone. In recent trials, active titration of the insulin dose to treatment target levels has been effective in improving the overall glycemic profile. Insulin glargine and insulin detemir, long-acting insulin analogues, are safe and effective and can be used initially as basal insulin with oral agents or with prandial insulin (regular human insulin or a rapid-acting insulin analogue [eg, insulin lispro, insulin aspart, insulin glulisine]) if glucose levels are not well controlled with basal insulin plus oral agents. Basal-prandial insulin regimens that utilize both long-acting and rapid-acting insulin analogues most closely resemble normal pancreatic insulin secretion and are effective in allowing patients to achieve recommended glycemic targets.

**Conclusions:** Early and persistent intensification of therapy designed to achieve glycemic goals, including the use of oral agents and/or insulin, should be initiated at diagnosis and appropriately titrated. The contributions of FPG and PPG to overall A1C should be closely monitored so that the most appropriate and effective treatment regimen may be implemented. (*Insulin*. 2006;1:148–157) Copyright © 2006 Excerpta Medica, Inc.

**Key words:** A1C, rapid-acting insulin analogue, fasting plasma glucose, hypoglycemia.

## INTRODUCTION

An estimated 20.8 million individuals in the United States (nearly 7% of the population) have diabetes mellitus (DM), the vast majority of which (90%–95%) have type 2 DM.<sup>1</sup> Although >14.6 million persons have been diagnosed with DM, it is estimated that ~6.2 million remain undiagnosed and thus remain untreated. An additional 41 million individuals have prediabetes (ie, impaired fasting glucose and/or impaired glucose tolerance [IGT]) and may convert to type 2 DM.<sup>1</sup>

The goal of this article was to define glycosylated hemoglobin (A1C) and address the contributions of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels to overall A1C. Elevated A1C levels correlate with an increased risk of cardiovascular disease (CVD) and other

complications, which are also reviewed here. Available therapies and therapeutic strategies are discussed, including the use of insulin when oral therapy alone has not maintained glycemic control.

## MATERIALS AND METHODS

English-language articles (1990–2006) were searched on the PubMed database using the following terms: *insulin, type 2 diabetes, early insulin use, A1C, and hemoglobin A1C*.

## ARE TREATMENT GOALS BEING MET?

The American Diabetes Association (ADA) treatment recommendations for glycemic control call for an A1C level of <7.0%, FPG level of 90 to 130 mg/dL, and peak PPG level of <180 mg/dL.<sup>2</sup> The American College of Endocrinology

(ACE) recommends an even lower A1C treatment target of  $\leq 6.5\%$ .<sup>3</sup> Regardless of this difference in recommended A1C levels, most experts agree that the target A1C level should be as close to normal (ie, 4.5%–6.0%) as possible without causing hypoglycemia or other adverse events.

According to the National Health and Nutrition Examination Survey (NHANES), however, only 49.8% of adults with DM in the United States are achieving the ADA target A1C level of  $<7.0\%$ .<sup>4</sup> Furthermore, only 7.3% of adults with DM achieve simultaneous control of plasma glucose levels and other measures of risk for CVD, such as blood pressure control and normal serum cholesterol levels.<sup>5</sup> Despite the abundance of treatment options that include several different classes of oral and injected antidiabetic medications as well as numerous types of insulin (both human and analogue with various time–action profiles), treatment goals are not being met in a large number of patients.

### IMPORTANCE OF MEASURING GLYCOSYLATED HEMOGLOBIN

Treatment goals in the consensus guidelines from the ADA and ACE refer to A1C as the determinant of optimal glycemic control.<sup>2,3</sup> Therefore, it is important to address the following basic questions: “What is A1C, and what does it measure?” and “How is it an indicator of glycemic control?”

**T**reatment goals in the consensus guidelines from the American Diabetes Association and the American College of Endocrinology refer to A1C as the determinant of optimal glycemic control.

### Definition of Glycosylated Hemoglobin

Approximately 90% of hemoglobin is adult-type hemoglobin A in adults with no hemoglobinopathies such as HbS or HbC traits, which consists of A<sub>0</sub> and the chemically modified subgroups A1C, A1B, A1A1, and A1A2. These minor components of hemoglobin A are slightly modified but provide a window through which the chemical makeup of blood can be measured. Hemoglobin A1C is a minor component of hemoglobin to which glucose is bound.

A1C values are directly proportional to the concentration of glucose in the blood over the full lifetime of the red blood cells and therefore reflect mean glycemia over the previous 90 to 120 days. Because of this, A1C values are not subject to the fluctuations that are seen with daily blood glucose monitoring.<sup>6</sup> Approximately 50% of the A1C value reflects the past 30 days and ~10% of the value reflects the preceding 90 to 120 days.<sup>6</sup>

### Rationale for Current Glycosylated Hemoglobin Targets

The current A1C goals are based on years of epidemiologic data and results of large prospective studies, including the United Kingdom Prospective Diabetes Study (UKPDS)

and the Diabetes Control and Complications Trial (DCCT).<sup>7–12</sup> In the 10-year follow-up to the UKPDS, patients with type 2 DM who were treated intensively had a mean A1C level of 7.0% (range, 6.2%–8.2%) and those treated conventionally had a mean A1C level of 7.9% (range, 6.9%–8.8%). Those patients with lower A1C levels had a 12% lower risk for any DM-related end point (eg, death from hyperglycemia or hypoglycemia, myocardial infarction, amputation, retinal coagulation) ( $P = 0.029$ ). The greatest reduction in risk (25%) came from a reduced possibility of microvascular end points ( $P < 0.01$ ), such as the need for retinal photocoagulation.<sup>10</sup> Furthermore, data from long-term follow-up of the DCCT—known as the Epidemiology of Diabetes Interventions and Complications Study—have revealed that patients with type 1 DM who originally achieved intensive glycemic control sustained benefits with respect to micro- and macrovascular disease risk despite subsequent lessening of glycemic control.<sup>13–15</sup> This suggests there is “metabolic memory,” as the physiologic benefits are sustained beyond the initial intensive period of glycemic control.

Data from the UKPDS demonstrated a correlation between A1C levels and the relative risk for DM complications. After following up 3642 patients for 10 years, UKPDS data showed that for each 1% reduction in A1C, there was a corresponding 21% decrease in any DM-related end point ( $P < 0.001$ ), including 21% in DM-related deaths ( $P < 0.001$ ), 14% in myocardial infarction ( $P < 0.001$ ), and 37% in microvascular complications ( $P < 0.001$ ).<sup>9</sup> The lowest risk of complications was associated with an A1C level  $<6\%$ . Interestingly, another study of 4662 men and 5570 women found that higher A1C levels were associated with mortality in patients with or without DM, regardless of age, body mass index, waist-to-hip ratio, systolic blood pressure, serum cholesterol, cigarette smoking, or history of CVD.<sup>7</sup> However, in an analysis after a mean 6-year follow-up that examined the association of A1C levels with mortality, the risk was 2 to 4 times greater in men with DM than in men without DM and ~1.5 to 2 times higher in those with prediabetes.<sup>8</sup> An increase in A1C of 1% was associated with an increased risk of 28% for death that was independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking.<sup>8</sup>

To monitor glycemic control and prevent DM-related CVD, A1C measurement is considered the gold standard in patients with DM.<sup>10,12</sup> The ADA and ACE guidelines call for regular assessment of glycemic control using periodic measurements of A1C levels.<sup>2,3</sup> Daily assessments of glycemic control should include regular self-monitoring of fasting preprandial and postprandial glucose levels to make appropriate adjustments in antidiabetic medications.

### Contribution of Fasting and Postprandial Glucose to Glycosylated Hemoglobin

It has been shown that A1C levels are strongly correlated with mean plasma glucose levels (Table I).<sup>6,16</sup> FPG levels are physiologically determined by the rate of hepatic glucose

**Table 1.** Correlation between glycosylated hemoglobin (A1C) and mean plasma glucose (MPG) levels.

A1C, %	Regression-Estimated MPG		Approximate MPG for Clinical Use	
	mmol/L	mg/dL	mmol/L	mg/dL
4.0	3.6	65	3.5	65
5.0	5.6	101	5.5	100
6.0	7.6	137	7.5	135
7.0	9.6	172	9.5	170
8.0	11.5	208	11.5	205
9.0	13.5	244	13.5	240
10.0	15.5	279	15.5	275
11.0	17.5	315	17.5	310
12.0	19.5	350	19.5	345

Copyright © 2002 American Diabetes Association. From *Diabetes Care*, Vol. 25, 2002:275–278.<sup>6</sup> Modified with permission from *The American Diabetes Association*.

production, which is a function of the rate of insulin production, hepatic sensitivity to insulin levels, and free fatty acid concentrations.<sup>17</sup> However, PPG levels or excursions are influenced by preprandial glucose level as well as meal-induced insulin secretion, meal glucose load, and sensitivity of peripheral tissue to insulin.<sup>11,18</sup> For maximal reduction of A1C, assessments of preprandial and postprandial glucose levels are necessary as part of a DM management program.

**F**or maximal reduction of A1C, assessments of preprandial and postprandial glucose levels are necessary as part of a DM management program.

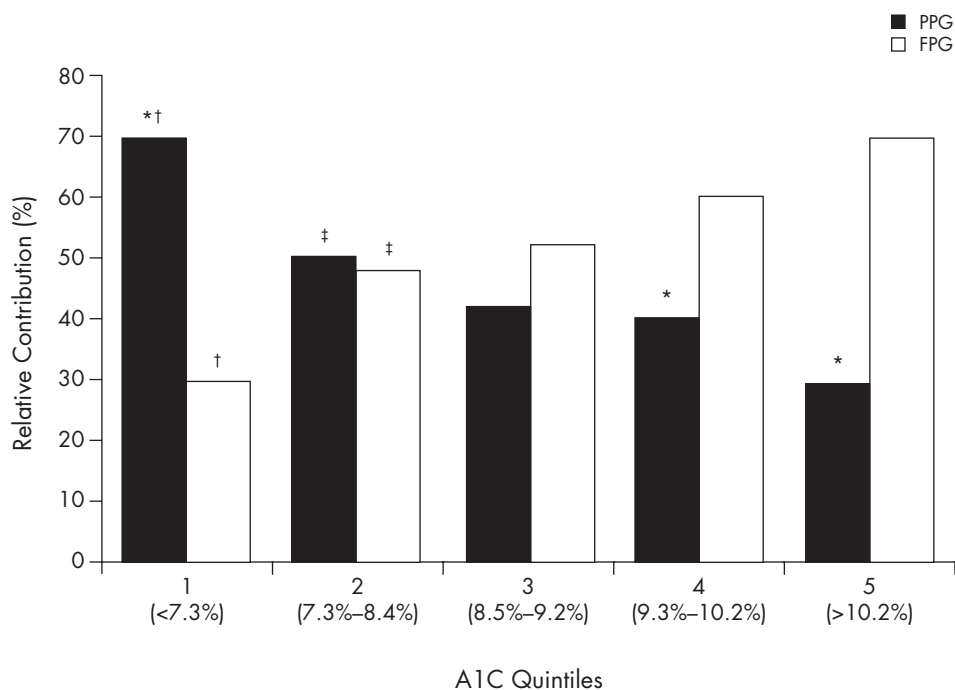
A recent study examined the relative contributions of FPG and PPG levels in relationship to A1C levels.<sup>16</sup> The researchers found that the relative contribution of PPG excursions to A1C levels is predominant in patients whose DM is well controlled, whereas the contribution of fasting hyperglycemia to A1C levels increases gradually as DM worsens. At lower A1C levels (ie, <7.3%), the contribution of PPG levels was 2 times greater than that of fasting hyperglycemia; however, for those patients with A1C levels >10.2%, the reverse was true. The contribution of fasting hyperglycemia to A1C levels was 2 times greater than the contribution of postprandial hyperglycemia (**Figure 1**).<sup>16</sup> The crossover from primarily postprandial to fasting hyperglycemia contribution occurred at an A1C level of ~8.4%. These results suggest that there is a continuous spectrum for the contribution of postprandial and fasting hyperglycemia to A1C levels, which correlates with progressive worsening of DM and glycemic control. This has important clinical implications because as a patient approaches the target A1C level of <7.0%, PPG becomes an increasingly significant consideration.<sup>16</sup>

### CARDIOVASCULAR RISK ASSOCIATED WITH HYPERGLYCEMIA

Elevated FPG levels are correlated with increased micro- and macrovascular disease risk.<sup>10,12,19–21</sup> Postprandial hyperglycemia is often neglected as a cardiovascular risk factor. However, several epidemiologic and cross-sectional studies have demonstrated a link between postglucose challenge or PPG elevations and heightened cardiovascular risk; other researchers have reviewed this topic.<sup>11,22,23</sup> A comprehensive meta-analysis revealed that isolated postprandial hyperglycemia (2-hour postprandial glucose >140 mg/dL), even with a normal FPG (<110 mg/dL), is associated with a cardiovascular event risk of 1.58 (95% CI, 1.19–2.10) relative to a fasting glucose level of 75 mg/dL.<sup>24</sup> Thus, postprandial hyperglycemia is an independent risk factor for development of CVD. Moreover, patients whose fasting glucose levels are below the threshold for a diagnosis of DM may still be at increased risk of experiencing the complications associated with elevated glucose levels.<sup>24</sup>

**P**atients whose fasting glucose levels are below the threshold for a diagnosis of DM may still be at increased risk of experiencing the complications associated with elevated glucose levels.

Other important studies that demonstrate the relationship between glycemic control and increased cardiac risk include the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, the Norfolk cohort of the European Prospective Investigation of Cancer (EPIC) study, the Cardiovascular Health Study, the NHANES II Mortality Study, the Funagata Diabetes Study, and the Hoorn Study.<sup>7,8,25–29</sup> All of these studies have shown



**Figure 1.** Relative contributions of postprandial and fasting hyperglycemia to the overall diurnal hyperglycemia according to quintiles of glycosylated hemoglobin (A1C). \*Significant difference was observed between postprandial plasma glucose (PPG) and fasting plasma glucose (FPG) (paired *t* test); †significantly different from all other quintiles (analysis of variance); ‡significantly different from quintile 5 (analysis of variance). Copyright © 2003 American Diabetes Association. From *Diabetes Care*, Vol. 26, 2003:881–885.<sup>16</sup> Reprinted with permission from *The American Diabetes Association*.

an association between increased risk for CVD and increasing fasting and postprandial glucose levels or elevated A1C. In the DECODE study, glucose levels after the 2-hour glucose challenge were better predictors of deaths from all causes ( $P < 0.001$ ) and risk of CVD ( $P < 0.005$ ) than were the fasting blood glucose (FBG) levels.<sup>25</sup> This study found that PPG is an independent risk factor for predicting mortality.

The Cardiovascular Health Study and the Norfolk cohort of the EPIC study demonstrated an association between increased risk for CVD and elevated glucose levels or A1C, respectively, for subjects who would not necessarily be classified as having DM according to the ADA guidelines.<sup>7,30</sup> However, the World Health Organization (WHO) definition includes impaired fasting glucose as well as IGT as the criteria for DM. Using this definition, the number of cases of CVD attributable to IGT or newly diagnosed DM was 3 times higher than the number ascertained by the ADA definition, which only includes FBG level as the criterion for diagnosing DM. Although the ADA criterion for diagnosing DM based on FBG levels is lower than that put forth by the WHO ( $>7.0$  mmol/L [126 mg/dL] vs  $>7.8$  mmol/L [140 mg/dL]), the contribution of a 2-hour glucose tolerance criterion ( $\geq 7.8$  mmol/L [140 mg/dL] and  $<11.1$  mmol/L [200 mg/dL]) in the WHO definition revealed a greater sensitivity for predicting CVD.<sup>30</sup> Similarly, the NHANES II

Mortality Study showed that the risk increase for all-cause mortality was 40% higher in adults with IGT (FBG,  $<140$  mg/dL; 2-hour glucose tolerance,  $>140$  to  $<199$  mg/dL) compared with adults with normal glucose tolerance.<sup>27</sup> Although the risk rose with increased glucose levels (fasting and postchallenge), these studies suggest that even moderate elevations in glucose levels can increase the risk of CVD and mortality.

The importance of IGT as a measure of risk for mortality and CVD was also shown in the Hoorn Study.<sup>28</sup> This trial revealed that the 2-hour glucose tolerance test was more sensitive than A1C levels at predicting the risk of death from all causes and CVD regardless of whether the subjects had DM. Even after excluding patients with newly diagnosed DM and known cardiovascular risk, a 2.20 and 3.00 relative risk for death from all causes and CVD, respectively, was associated with a 5.8-mmol/L (104-mg/dL) increase above normal in postchallenge glucose levels.<sup>28</sup>

### Mechanisms Underlying Hyperglycemia and Cardiovascular Damage

The proposed mechanisms by which increases in plasma glucose levels may produce cardiovascular damage involve inflammation and oxidative stress (Figure 2).<sup>11,31–33</sup> Increased glucose uptake by cells ultimately results in acti-

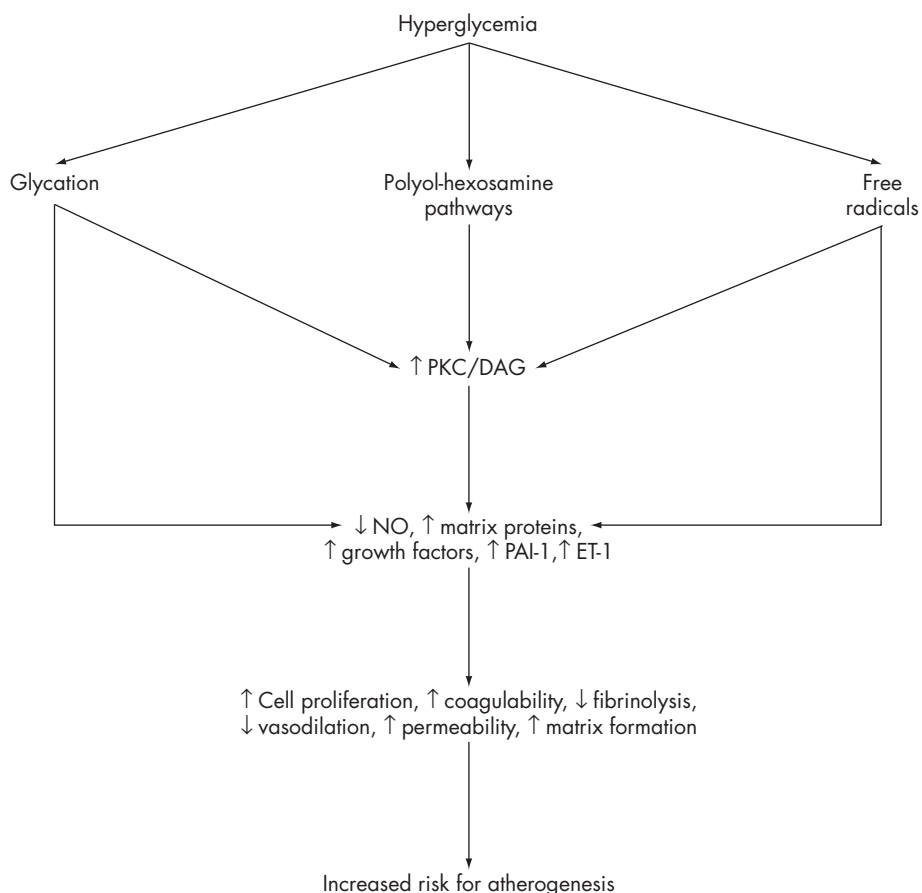
vation of diacylglycerol and protein kinase C, which in turn can decrease nitric oxide (a vasodilator) and increase endothelin-1 and plasminogen activator inhibitor-1 (which may lead to increased vascular contractility and coagulation).<sup>11,32</sup> In addition, glycosylation of extracellular proteins, such as low-density lipoprotein, renders them even more atherosclerotic and subject to increased oxidation.<sup>11</sup> Hyperglycemia also increases the generation of free radicals, which could further contribute to abnormalities in the proteins involved with coagulation and vascular health.<sup>11</sup> The end result is an increase in cell proliferation, coagulability, vascular permeability, and matrix formation and a decrease in fibrinolysis and vasodilation, which are known factors for increased risk of atherosclerosis.<sup>11</sup>

type 2 DM.<sup>10,34,35</sup> The optimal, individualized use of these agents must address the challenge of how to achieve both fasting and postprandial glucose control.<sup>22</sup> Therapy typically begins with oral monotherapy or combination therapy with metformin. If necessary, the addition of a sulfonylurea, thiazolidinedione, or incretin mimetic agent to a metformin-based regimen can help patients achieve glycemic control and may delay the need for insulin therapy.<sup>36,37</sup> Indeed, with proper nutrition and exercise, many patients can maintain glycemic control over a long period of time with oral antidiabetic therapy. However, when oral therapy is no longer sufficient to maintain glycemic control, insulin therapy should be considered.

**ATTAINING OPTIMAL CONTROL OF FASTING AND POSTPRANDIAL GLUCOSE LEVELS**

Because fasting and postprandial glucose control are essential for reducing cardiovascular risk, insulin therapy alone or in combination with oral agents is highly effective treatment for improving long-term glycemic control in patients with

**W**ith proper nutrition and exercise, many patients can maintain glycemic control over a long period of time with oral antidiabetic therapy. However, when oral therapy is no longer sufficient to maintain glycemic control, insulin therapy should be considered.



**Figure 2.** Mechanisms by which hyperglycemia may increase risk of macrovascular disease. PKC = protein kinase C; DAG = diacylglycerol; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; ET-1 = endothelin-1. Reprinted with permission from Gerich.<sup>11</sup>

A stepwise approach to the initiation of insulin therapy can begin with adding basal insulin to the existing oral therapy regimen.<sup>35</sup> This strategy allows for the addition and initiation of a QD insulin dose to achieve A1C target levels. Basal insulin therapy corrects FPG levels but also improves the overall glycemic profile.<sup>38</sup> Basal insulin therapy can also lower postprandial glucose levels because the baseline fasting glucose, on which prandial glucose excursions are superimposed, is lowered.<sup>35,39</sup> The most commonly used options for basal insulin are neutral protamine Hagedorn (NPH) insulin and insulin glargine. Recently, insulin detemir, a long-acting insulin analogue, has received approval from the US Food and Drug Administration for use as a basal insulin. NPH, an intermediate-acting insulin, typically has a pronounced peak effect within 4 to 10 hours of administration before returning to baseline levels within 10 to 16 hours.<sup>35,40</sup> In contrast, insulin glargine and insulin detemir are long-acting insulin analogues. Insulin glargine provides insulin delivery over a 24-hour period with no pronounced peak.<sup>35,40</sup> Insulin detemir appears to have a relatively shorter time-action profile, which necessitates BID injections in patients with type 1 DM.<sup>41</sup>

Several studies have demonstrated that basal insulin can be titrated safely and effectively to attain glycemic control.<sup>34,42-44</sup> Although insulin glargine and NPH insulin can be used to achieve A1C targets, insulin glargine has been shown to cause significantly fewer episodes of hypoglycemia compared with NPH insulin, including severe hypoglycemia ( $P < 0.045$ ) and nocturnal hypoglycemia ( $P < 0.001$ ), thus removing a considerable barrier to the initiation and use of insulin.<sup>45</sup>

The Treat-to-Target Trial demonstrated the efficacy of QD basal insulin therapy in combination with oral therapy.<sup>34</sup> In this study, a single bedtime injection of long-acting insulin (insulin glargine or NPH insulin) was added to the preexisting oral antidiabetic treatment regimen.<sup>34</sup> The insulin dose was systematically titrated until a defined fasting glucose target of  $\leq 100$  mg/dL was achieved (Table II).<sup>34</sup> During the 24 weeks of treatment, insulin glargine and NPH insulin treatment substantially lowered A1C levels, with 58.0% and 57.3% of patients, respectively, achieving A1C levels  $\leq 7.0\%$ . However, more patients in the insulin glargine group than in the NPH insulin group reached target A1C levels without any episodes of hypoglycemia (33.2% vs 26.7%;  $P < 0.05$ ).<sup>34</sup> Nearly 25% more patients treated with insulin glargine than with NPH insulin reached target A1C levels of  $\leq 7.0\%$  without nocturnal hypoglycemia. Moreover, the overall incidence of any hypoglycemic event (eg, plasma-referenced glucose  $< 72$  mg/dL) and severe hypoglycemia (eg, patient required assistance of another person, and had a glucose level of  $< 56$  mg/dL or prompt recovery after glucose or glucagon use) was lower with insulin glargine than with NPH insulin.<sup>34</sup> Furthermore, this study demonstrated the importance of actively titrating the insulin dose to target FBG levels for patients to achieve glycemic control. An alternative titration scheme has recently been validated; patients

**Table II.** Forced weekly insulin titration schedule.

Start with 10 IU/d bedtime basal insulin and adjust weekly

Mean of Self-Monitored FPG Values from Preceding 2 Days	Increase in Insulin Dose, IU/d*†
$\geq 180$ mg/dL (10.0 mmol/L)	8
140–180 mg/dL (7.8–10.0 mmol/L)	6
120–140 mg/dL (6.7–7.8 mmol/L)	4
100–120 mg/dL (5.6–6.7 mmol/L)	2

FPG = fasting plasma glucose.

\*The treat-to-target FPG level was  $\leq 100$  mg/dL. Exceptions to this algorithm were: (1) No increase in dosage if plasma-referenced glucose  $< 72$  mg/dL was documented at any time in the preceding week; and (2) in addition to no increase, small insulin dose decreases (ie, 2–4 IU/d per adjustment) were allowed if severe hypoglycemia (requiring assistance) or plasma-referenced glucose  $< 56$  mg/dL were documented in the preceding week.

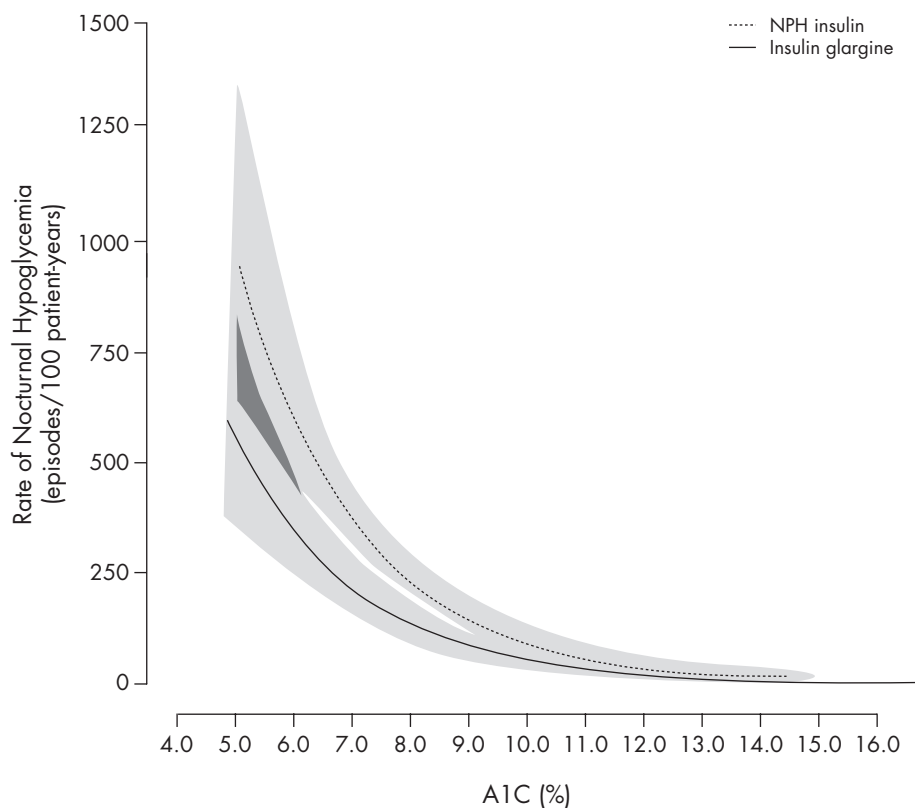
†An alternative titration scheme has been recently validated by instructing patients to increase their insulin glargine dosage by 2 units every 3 days (or twice a week) until a mean FPG of 100 mg/dL is achieved.<sup>46</sup>

Copyright © 2003 American Diabetes Association. From *Diabetes Care*, Vol. 26, 2003:3080–3086.<sup>34</sup> Reprinted with permission from *The American Diabetes Association*.

are instructed to increase their insulin glargine dosage by 2 units every 3 days (or twice a week) until a mean FPG of 100 mg/dL is achieved.<sup>46</sup>

A recent meta-analysis of controlled trials of similar design for insulin glargine versus NPH insulin QD or BID in adults with type 2 DM confirmed that insulin glargine given QD reduces the risk of hypoglycemia compared with NPH insulin.<sup>45</sup> This finding facilitates more aggressive insulin treatment to an A1C target of  $\leq 7.0\%$ . These results are consistent with an earlier meta-analysis that determined the relationship between A1C and hypoglycemia for 1786 patients with type 2 DM.<sup>47</sup> The investigators concluded that at equivalent rates of either confirmed symptomatic hypoglycemia or confirmed nocturnal hypoglycemia, use of insulin glargine was associated with lower A1C levels compared with NPH (Figure 3).<sup>47</sup>

When necessary, prandial insulin (regular human insulin [RHI] or a rapid-acting insulin analogue) can be added to the appropriate meal or meals when basal insulin in combination with oral agents is no longer sufficient to provide adequate glycemic control.<sup>35</sup> This offers a simple, straightforward, and stepwise approach to correcting fasting and postprandial glucose excursions in patients with type 2 DM. Therapeutic options for prandial insulin include short-acting RHI or the newer rapid-acting insulin analogues. Currently available rapid-acting insulin analogues include insulin lispro, insulin aspart, and insulin glulisine. The use



**Figure 3.** Assessment of the relationship between glycosylated hemoglobin (A1C) and nocturnal hypoglycemia, based on use of insulin glargine versus neutral protamine Hagedorn (NPH) insulin. Shading in the graphic indicates CIs. Copyright © 2003 American Diabetes Association. From *Diabetes*, Vol. 52, Supplement 1, 2003.<sup>47</sup> Reprinted with permission from *The American Diabetes Association*.

of basal insulin combined with a rapid-acting insulin analogue overcomes the difficulty of optimally controlling postprandial hyperglycemia that is associated with RHI formulations. The rapid-acting analogues have a faster onset of action (typically 5–15 minutes) and a shorter duration of action (typically 4–6 hours) compared with RHI.<sup>40</sup> The rapid-acting insulin analogues, therefore, have time–action profiles that approach normal pancreatic insulin secretion at mealtimes; in combination with a basal insulin, these analogues provide a more physiologic insulin response to postprandial glucose excursions.<sup>35</sup>

Alternatively, basal-prandial therapy can be initiated by using premixed or split-mixed insulin formulations (eg, 70/30 NPH insulin/RHI).<sup>35,48</sup> Although premixed insulin preparations offer the convenience of BID insulin administration (ie, in the morning and in the evening), these formulations increase the risk of hypoglycemia because they require fixed dosing without titration of individual components and do not allow for mealtime flexibility.<sup>40,49</sup> Furthermore, these formulations do not approximate physiologic basal and prandial coverage as well as the use of a rapid-acting insulin analogue in combination with a basal insulin such as insulin glargine, insulin detemir, or NPH.<sup>35</sup>

## INSULIN PUMP THERAPY

Insulin pump therapy (also called continuous subcutaneous insulin infusion [CSII]) is a very flexible and effective method to approximate physiologic insulin dynamics. This therapeutic option may be associated with additional advantages, such as the ability to rapidly respond to hypoglycemia and changes in physical activity. CSII users must have the motivation and the ability to frequently test their glucose levels, as well as the decision-making skills to adjust therapy based on the results of the monitoring data.<sup>50</sup>

## CONCLUSIONS

A1C is the gold standard for assessing and monitoring glycemic control in patients with DM. Given the close association between elevated A1C levels and the increased risk of CVD and other DM complications, A1C provides a measure of how well FPG and PPG levels are within recommended guidelines. However, because measurement of A1C does not discriminate between the respective contributions of fasting and postprandial glycemia, continuous self-monitoring of blood glucose levels is important to distinguish between the FPG and postprandial contribution to hyperglycemia.

Several studies have shown a correlation of postprandial glucose levels with cardiovascular risk, and it is therefore important for the insulin therapy regimen to correct fasting and postprandial glucose excursions. Basal insulin therapy provides a reduction in FPG levels as well as a lowering of the overall glycemic profile. When basal insulin therapy, in combination with oral agents, is no longer sufficient, it may become necessary to add a prandial insulin to prevent postprandial hyperglycemia. Given all the available options for controlling hyperglycemia—including oral agents, insulin analogues, and emerging therapies—the therapeutic decision-making process may appear complex. Fortunately, with the current expansion of the options to treat DM and its complications, patient and physician can work together as a team to determine the best therapy to obtain optimal glycemic control.

### ACKNOWLEDGMENTS

The author gratefully acknowledges the scientific staff of Embryon Inc. (Somerville, New Jersey) who assisted in the preparation of a first draft of this article based on an author-approved outline and also assisted in implementing author revisions. Embryon Inc. supports the Good Publication Practice working group guidelines on the role of medical

writers in developing scientific publications ([www.gpp-guidelines.org](http://www.gpp-guidelines.org)).

The following is a summary of the author's relationships with any pharmaceutical company. Member of the speakers' bureau (now or in the past): Bristol-Myers Squibb Company (New York, New York); Aventis Pharmaceuticals Inc. (Bridgewater, New Jersey); Pfizer Inc. (New York, New York); Merck & Co., Inc. (Whitehouse Station, New Jersey); Merck Santé (Lyon, France); GlaxoSmithKline (Research Triangle Park, North Carolina); Eli Lilly and Company (Indianapolis, Indiana); and Amylin Pharmaceuticals, Inc. (San Diego, California). Investigator (now or in the past): Bristol-Myers Squibb Company; sanofi-aventis U.S. (Bridgewater, New Jersey); GlaxoSmithKline; Merck & Co., Inc.; Schering-Plough Corporation (Kenilworth, New Jersey); Takeda Pharmaceuticals North America, Inc. (Deerfield, Illinois); Eli Lilly and Company; Amylin Pharmaceuticals, Inc.; Forest Laboratories, Inc. (New York, New York); Becton, Dickinson and Company (Franklin Lakes, New Jersey); Novo Nordisk A/S (Bagsvaerd, Denmark); Pharmacia & Upjohn, Inc. (Peapack, New Jersey); Pfizer Inc.; and Roche Diagnostics (Basel, Switzerland). Occasional consultant: Bristol-Myers Squibb Company; Aventis Pharmaceuticals Inc.; GlaxoSmithKline; Amylin Pharmaceuticals, Inc.; Eli Lilly and Company; Pfizer Inc.; and Merck & Co., Inc.

### REFERENCES

- Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2005. Atlanta, Ga: US Dept of Health and Human Services, Centers for Disease Control and Prevention; 2005. Available at: [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2005.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf). Accessed March 15, 2006.
- American Diabetes Association. Standards of medical care in diabetes [published correction appears in *Diabetes Care*. 2005;28:990]. *Diabetes Care*. 2005;28(Suppl 1):S4–S36.
- American College of Endocrinology. Consensus statement on guidelines for glycemic control. *Endocr Pract*. 2002;8(Suppl 1):5–11.
- Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among US adults with diabetes, 1999–2002: The National Health and Nutrition Examination Survey. *Diabetes Care*. 2006;29:531–537.
- Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*. 2004;291:335–342.
- Rohlfing CL, Wiedmeyer HM, Little RR, et al. Defining the relationship between plasma glucose and HbA(1c): Analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care*. 2002;25:275–278.
- Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: The European Prospective Investigation into Cancer in Norfolk. *Ann Intern Med*. 2004;141:413–420.
- Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ*. 2001;322:15–18.
- 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.
- 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) [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837–853.
- Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163:1306–1316.
- 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.
- Nathan DM, Lachin J, Cleary P, et al, for the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med*. 2003;348:2294–2303.
- The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes

- four years after a trial of intensive therapy. *N Engl J Med*. 2000;342:381–389.
15. Nathan DM, Cleary PA, Backlund JY, et al, for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643–2653.
  16. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA<sub>1c</sub>. *Diabetes Care*. 2003;26:881–885.
  17. Riddle MC. Evening insulin strategy. *Diabetes Care*. 1990;13:676–686.
  18. Carroll MF, Izard A, Riboni K, et al. Fasting hyperglycemia predicts the magnitude of postprandial hyperglycemia: Implications for diabetes therapy. *Diabetes Care*. 2002;25:1247–1248.
  19. Tanne D, Koren-Morag N, Goldbourt U. Fasting plasma glucose and risk of incident ischemic stroke or transient ischemic attacks: A prospective cohort study. *Stroke*. 2004;35:2351–2355.
  20. Goldberg RB, Mellies MJ, Sacks FM, et al, for the Care Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: Subgroup Analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation*. 1998;98:2513–2519.
  21. Laakso M, Lehto S. Epidemiology of macrovascular disease in diabetes. *Diabetes Rev*. 1997;5:294–315.
  22. Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in type 2 diabetes? *Eur J Clin Invest*. 2000;30(Suppl 2):3–11.
  23. Bonora E, Muggeo M. Postprandial blood glucose as a risk factor for cardiovascular disease in type II diabetes: The epidemiological evidence. *Diabetologia*. 2001;44:2107–2114.
  24. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22:233–240.
  25. DECODE Study Group and the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: Comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med*. 2001;161:397–405.
  26. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care*. 1999;22:920–924.
  27. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447–453.
  28. de Vegt F, Dekker JM, Ruhe HG, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: The Hoorn Study. *Diabetologia*. 1999;42:926–931.
  29. Hanefeld M, Koehler C, Schaper F, et al. Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis*. 1999;144:229–235.
  30. Barzilay JI, Spiekerman CF, Wahl PW, et al. Cardiovascular disease in older adults with glucose disorders: Comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria. *Lancet*. 1999;354:622–625.
  31. Lebovitz HE. Effect of the postprandial state on nontraditional risk factors. *Am J Cardiol*. 2001;88:20H–25H.
  32. King GL, Wakasaki H. Theoretical mechanisms by which hyperglycemia and insulin resistance could cause cardiovascular diseases in diabetes. *Diabetes Care*. 1999;22(Suppl 3):C31–C37.
  33. Lipinski B. Pathophysiology of oxidative stress in diabetes mellitus. *J Diabetes Complications*. 2001;15:203–210.
  34. 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.
  35. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: Scientific review. *JAMA*. 2003;289:2254–2264.
  36. Dailey GE, Noor MA, Park JS, et al. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: A randomized, double-blind trial. *Am J Med*. 2004;116:223–229.
  37. 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. *Diabetes Care*. 2006;29:1963–1972.
  38. Riddle MC. Making the transition from oral to insulin therapy. *Am J Med*. 2005;118(Suppl 5A):14S–20S.
  39. Dailey G. New strategies for basal insulin treatment in type 2 diabetes mellitus. *Clin Ther*. 2004;26:889–901.
  40. Hirsch IB. Insulin analogues. *N Engl J Med*. 2005;352:174–183.
  41. Bott S, Tusek C, Jacobsen LV, et al. Insulin detemir reaches steady-state after the first day of treatment and shows a peakless time-action profile with twice daily-applications. Presented at: 18th Congress of the International Diabetes Federation; August 24–29, 2003; Paris, France. Abstract 785.
  42. Ratner RE, Hirsch IB, Neifing JL, et al, for the US Study Group of Insulin Glargine in Type 1 Diabetes. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care*. 2000;23:639–643.
  43. Raskin P, Klaff L, Bergenstal R, et al. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care*. 2000;23:1666–1671.
  44. Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-Week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care*. 2001;24:631–636.
  45. Rosenstock J, Dailey G, Massi-Benedetti M, et al. Reduced hypoglycemia risk with insulin glargine: A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care*. 2005;28:950–955.
  46. Davies M, Storms F, Shutler S, et al, for the ATLANTUS Study Group. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: Comparison of two treatment algorithms using insulin glargine. *Diabetes Care*. 2005;28:1282–1288.

47. Yki-Jarvinen H, Haring H-U, Johnson E, et al. The relationship between glycemic control and hypoglycemia using insulin glargine versus NPH insulin: A meta-regression analysis in type 2 diabetes. *Diabetes*. 2003;52(Suppl 1). Abstract 642-P.
48. Bell DS. Type 2 diabetes mellitus: What is the optimal treatment regimen? *Am J Med*. 2004;116(Suppl 5A):23S-29S.
49. Raskin P, Allen E, Hollander P, et al, for the INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: A comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005;28:260-265.
50. Bode BW, Sabbah HT, Gross TM, et al. Diabetes management in the new millennium using insulin pump therapy. *Diabetes Metab Res Rev*. 2002;18(Suppl 1):S14-S20.

**Address correspondence to:** George E. Dailey, MD, Division of Diabetes and Endocrinology, Scripps Clinic, 10666 N. Torrey Pines Road, La Jolla, CA 92037. E-mail: gdailey@scrippsclinic.com