

# Overview of insulin replacement therapy

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### Disclosure

*Dr Wright has disclosed that he is on the advisory boards for Amylin Pharmaceuticals, Inc., Eli Lilly and Company, and Novo Nordisk Inc. and the speakers bureaus for Amylin Pharmaceuticals, Inc., and Eli Lilly and Company.*

## Importance of tight glycemic control for avoiding diabetes complications

Tight glycemic control is variously defined in clinical trials, but a glycosylated hemoglobin (A1C) value <7% is often set as a target for treatment, which is consistent with the American Diabetes Association (ADA) goals for patients with diabetes.<sup>1</sup> Although this goal may seem aggressive and is difficult for many patients to reach,<sup>2</sup> this value is substantially higher than that for patients without diabetes, whose A1C range is typically 4% to 6%.<sup>3</sup>

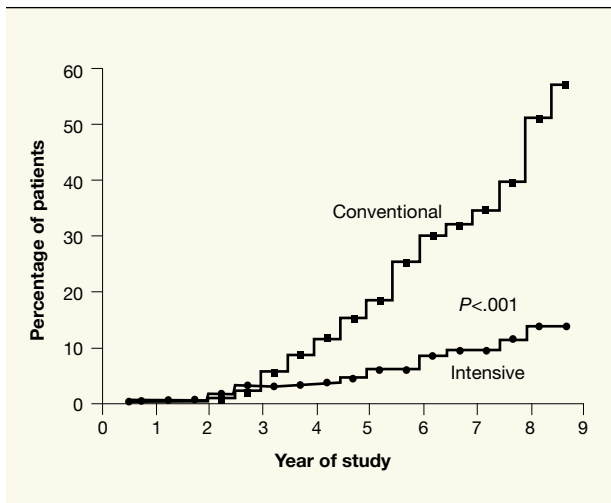
Achieving and maintaining tight glycemic control is important for avoiding, delaying, and/or decreasing the severity of long-term complications of diabetes. Long-standing diabetes can lead to irreversible organ damage, including cardiovascular disease, renal dysfunction, ocular impairment, and neuropathies that involve both sensory nerve fibers and the autonomic nervous system.<sup>4-8</sup> Results from landmark studies have demonstrated that tight glycemic control can decrease the risk for long-term complications in patients with type 1 or type 2 diabetes (FIGURES 1 AND 2).<sup>9-12</sup>

Although landmark studies have demonstrated important benefits of tight glycemic control in patients with type 1 or type 2 diabetes, initial results of recent studies challenged the knowledge that intensive therapy is invariably associated with lower A1C levels and better clinical outcomes for patients with type 2 diabetes. In a study of patients with type 2 diabetes following myocardial infarction (MI), the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 2) investigation<sup>13</sup> did not find any significant clinical or metabolic benefit of an acutely introduced, long-term insulin treatment program compared with conventional management. Similarly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study<sup>14</sup> showed that, as compared with standard therapy, the use of intensive therapy to target an A1C level of <6% did not significantly reduce major cardiovascular events; rather, it increased mortality vs treatment aimed at an A1C goal of 7% to 7.9% in patients with high-risk diabetes. Two other recent studies, the Action in Diabetes and Vascular Disease (ADVANCE) study<sup>15</sup> and the Veterans Affairs Diabetes Trial (VADT)<sup>16</sup> have also indicated that intensive therapy (targeted at an A1C level ≤6.5% in ADVANCE and an A1C reduction of ≥1.5% in VADT) does not decrease cardiovascular mortality or events in patients with diabetes.

Experts in the care of patients with diabetes and cardiovascular disease

**FIGURE 1**

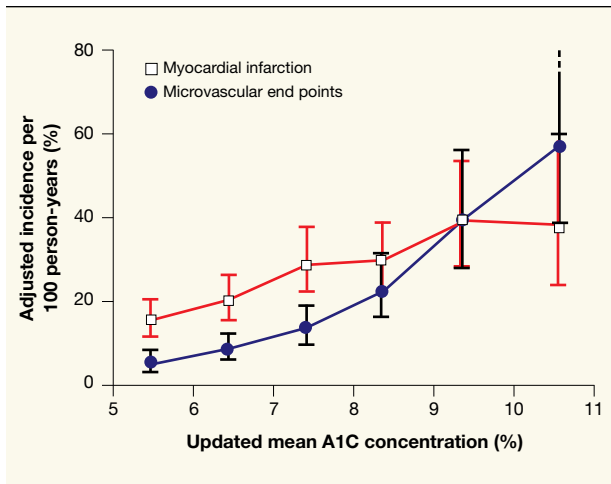
**Intensive glycemc control and risk for microvascular complications**



Intensive glycemc control decreased the risk for microvascular complications in patients with type 1 diabetes by 76%: cumulative incidence of retinopathy in the primary prevention cohort, assessed at years 3, 5, 7, and 9. Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977-986. Copyright © 1993 Massachusetts Medical Society. All rights reserved.

**FIGURE 2**

**Intensive glycemc control and risk for MI and microvascular complications**



A1C, glycosylated hemoglobin; MI, myocardial infarction. Intensive glycemc control decreased the risk for macrovascular (myocardial infarction) and microvascular complications in white male patients aged 50 to 54 years at diagnosis with a mean duration of type 2 diabetes of 10 years. Each point shows the risk for myocardial infarction or microvascular end points as a function of A1C over the follow-up period. Bars represent 95% confidence intervals.

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recently reevaluated the results from the ACCORD, ADVANCE, and VADT studies<sup>17</sup> and concluded that these studies did, in fact, indicate a benefit of tight glycemc control in the primary prevention of cardiovascular events. This review also suggested multiple potential explanations for the increased mortality seen with tight glycemc control in ACCORD vs other trials that did not have such a result. These explanations included the participation of patients with more advanced diabetes in the ACCORD trial, more rapid lowering of A1C levels in ACCORD vs the other studies, and a potentially increased risk for severe hypoglycemia that contributed to cardiovascular mortality.<sup>17</sup> This group also reaffirmed an A1C level <7% as the treatment goal for patients with diabetes.<sup>17</sup> However, less stringent goals might be suitable for patients with a history of severe hypoglycemia, limited life expectancy, or advanced diabetes complications, or for those with long-standing diabetes who have great difficulty achieving A1C levels <7% despite appropriate education and care.<sup>17</sup> Thus, treatment must be individualized on the basis of patient characteristics.

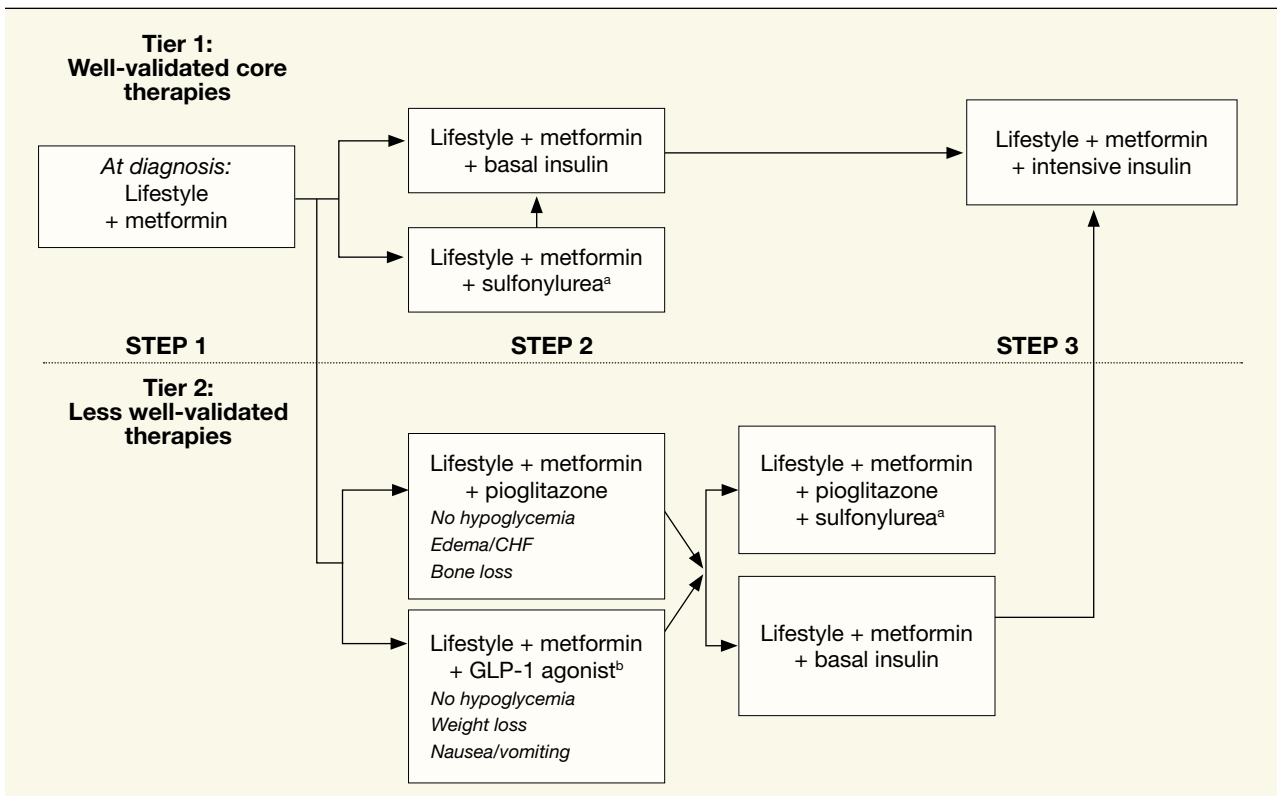
**The role of FPG and PPG in risk for complications**

Fasting plasma glucose (FPG) and postprandial glucose (PPG) both contribute to the risk for diabetes complications. PPG is believed to be a particularly important determinant of macrovascular risk in patients with diabetes. Results from the Honolulu Heart Study<sup>18</sup> showed that elevated 1-hour PPG is a strong predictor of risk for coronary heart disease mortality. Results from this study showed that men in the fourth quintile of postchallenge glucose (157-189 mg/dL) had twice the age-adjusted risk of fatal coronary heart disease vs those in the lowest quintile (40-114 mg/dL).

Assessment of the effects of therapy aimed at lowering PPG in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial<sup>19</sup> indicated that treatment with acarbose (100 mg administered 3 times per day) was associated with decreased risk for silent MI vs placebo in patients with impaired glucose tolerance. This study also demonstrated that reducing PPG with acarbose was associated with a 49% relative risk reduction for the occurrence of cardiovascular events and a 91% decrease in the risk for MI. Treatment with acarbose also resulted in a 34% decline in the relative risk for development of

**FIGURE 3**

**The American Diabetes Association and European Association for the Study of Diabetes algorithm for the management of type 2 diabetes**



CHF, congestive heart failure; GLP, glucagon-like peptide.

<sup>a</sup> Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.

<sup>b</sup> Insufficient clinical use to be confident regarding safety.

Lifestyle intervention should be reinforced at every visit. Glycosylated hemoglobin (A1C) should be checked every 3 months until the A1C is <7% and at least every 6 months thereafter. Nathan DM, et al. Copyright © 2009 American Diabetes Association. From *Diabetes Care*, Vol. 32; 2009, 193-203. Reprinted with permission from The American Diabetes Association.

hypertension.<sup>20</sup> The Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes (HEART2D) study<sup>21</sup> determined the effects of PPG control on cardiovascular outcomes in patients who had had an MI within the 21 days before study enrollment. The trial compared two treatment strategies: (1) a postprandial strategy—premeal insulin lispro with basal insulin at bedtime if needed (neutral protamine Hagedorn [NPH] insulin), targeting 2-hour PPG  $\leq 7.5$  mmol/L ( $\leq 135$  mg/dL), and (2) a basal strategy—NPH insulin twice daily or insulin glargine once daily, or premixed human insulin (70% NPH/30% regular insulin) twice daily, targeting FPG and premeal blood glucose  $\leq 6.7$  mmol/L ( $\leq 120$  mg/dL). Both groups targeted an A1C level of <7%. Study results presented in 2008<sup>22</sup> indicated no significant between-group difference for

cardiovascular outcomes.

The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial<sup>23</sup> is being carried out to determine whether normoglycemia achieved with the long-acting insulin analog, insulin glargine, can reduce cardiovascular morbidity and/or mortality in people with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes who are at high risk for vascular disease.

**ADA/EASD goals and treatment guidelines for type 2 diabetes**

As stated above, the ADA/EASD has established an A1C goal of <7.0% for adults with diabetes.<sup>24</sup> To achieve that goal, the initial recommended treatment for patients with type 2 diabetes is a combination of lifestyle chang-

es and metformin (**FIGURE 3**).<sup>24</sup> If an A1C level <7% is not achieved within 2 to 3 months, the recommended second step is the addition of either a basal insulin or a sulfonylurea to the treatment regimen. The third step for validated core therapies is to start or intensify insulin therapy.<sup>24</sup>

### Progressive nature of type 2 diabetes and loss of efficacy of oral antidiabetic drugs

In type 2 diabetes, there is not only impaired insulin secretion but also a progressive decline in  $\beta$ -cell function as well as chronic insulin resistance. Patients with this disease experience a reduction in islet and/or insulin-containing cell mass or volume.<sup>25</sup> Oral agents commonly prescribed for patients with type 2 diabetes do not prevent the progressive loss of  $\beta$ -cell function that is a feature of this disease.<sup>26</sup> The loss of  $\beta$ -cell function is correlated with increasing A1C levels and disease progression, which was demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS).<sup>27</sup> The progressive nature of type 2 diabetes mandates a corresponding evolution of treatment. Most patients will ultimately require insulin therapy to maintain glycemic control.<sup>28</sup>

### Current diabetes management: Achievement and maintenance of glycemic control

There has been a gradual improvement in the achievement of glycemic control by patients with diabetes. However, results from the National Health and Nutrition Surveys (NHANES) indicate that current treatment still does not achieve glycemic control in a large percentage of patients. The rate of glycemic control, as defined by an A1C level <7%, increased from 35.8% in 1999 to only 57.1% in 2004.<sup>29</sup> Thus, despite a gradual improvement, antidiabetic therapy still fails to achieve the ADA/EASD target in more than 40% of patients.

### When do patients with type 2 diabetes become candidates for insulin therapy?

The most recent guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recognize that insulin is the most effective diabetes medication for lowering hyperglycemia.<sup>24</sup> As noted above, the ADA/EASD treatment al-

gorithm now suggests that basal insulin can be added to the treatment regimen when a patient's A1C level remains  $\geq 7\%$  with lifestyle interventions and treatment with metformin.<sup>24</sup> Insulin may also be added when a combination of oral agents (eg, metformin and a sulfonylurea) does not maintain the A1C level at <7%. The ADA/EASD guidelines also recommend that insulin therapy be initiated immediately in patients with (1) severely uncontrolled diabetes with catabolism, defined as FPG >250 mg/dL, random glucose levels consistently >300 mg/dL, A1C >10%, or the presence of ketonuria; or (2) symptomatic diabetes with polyuria, polydipsia, and weight loss.<sup>24</sup>

Studies have shown that taking appropriate steps to achieve and maintain glycemic control can reduce the risk for long-term disease complications<sup>9-12</sup>; therefore, failure to take these steps, including failure to initiate insulin when necessary, and the resulting hyperglycemia likely increase the risk for long-term disease complications.

### Insulin preparations

The evolution of insulin preparations has greatly enhanced both the efficacy and safety of antihyperglycemic therapy.

#### Human insulins

Regular human insulin has been used to control prandial glucose (PG) excursions for many years, but because of its slow absorption and delayed onset of action,<sup>30</sup> it must be administered  $\geq 30$  minutes before meals.<sup>31</sup> Regular human insulin is also limited by the fact that absorption is variable and, therefore, it has variable efficacy in controlling PPG. The essential limitation of human insulin is that its pharmacokinetic/pharmacodynamic profile does not match that of physiologic insulin secretion in response to a meal.<sup>32</sup>

NPH, an intermediate-acting insulin, is generally used to provide a basal insulin level over the course of the day. However, the pharmacodynamic profile for this preparation poorly approximates physiologic insulin secretion.<sup>33</sup>

The onset of action of NPH begins approximately 2 to 4 hours after subcutaneous injection. There is a peak between 4 and 10 hours after injection that is followed by a slow decline. The total duration of action

for NPH insulin is 12 to 18 hours. Absorption of NPH insulin is also variable, both within and across patients.

Human insulins are also available in premixes designed to decrease the total number of daily injections required to control PG. These preparations may be useful in some patients because of their simplified dosing regimens. However, the pharmacokinetics for these preparations do not closely mimic patterns of physiologic insulin release, and they increase the risks of postprandial hyperglycemia and hypoglycemia.<sup>34</sup> Some of the limitations of premixed insulins have been addressed by using newer insulin analogs in these preparations (see below).

### Insulin analogs

Structural modifications made to the human insulin molecule have led to the development of insulin analogs. These structural modifications have resulted in improved pharmacokinetic/pharmacodynamic profiles that more closely mimic physiological insulin secretion, as well as improvements in efficacy and safety.<sup>35</sup> Currently available insulin analogs and premixes of these agents are listed in the **TABLE**.<sup>36</sup>

#### Rapid-acting insulin analogs

Rapid-acting insulin analogs more closely mimic physiologic insulin secretion compared with regular human insulin with respect to pharmacokinetic/pharmacodynamic profile, more rapid onset and shorter duration of action, greater peak effect, and better control over PPG.<sup>35-37</sup> When given at mealtimes, insulin lispro has consistently proven to be more effective than regular human insulin in lowering PPG. In addition, mealtime administration of insulin lispro improves glycemic control and reduces the risk for hypoglycemia compared with regular human insulin.<sup>38-41</sup> Insulin aspart has also been shown to provide improved control of PPG and reduced risk for hypoglycemia when compared with regular human insulin.<sup>42,43</sup> The third rapid-acting insulin analog currently available, insulin glulisine, has demonstrated improved or equivalent effects on 2-hour PPG excursions and overall glycemic control compared with regular human insulin.<sup>44</sup>

#### Long-acting insulin analogs

The 2 long-acting insulin analogs currently available are insulin glargine and insulin detemir. These agents have improved pharmacokinetic and pharmacody-

**TABLE**

**Insulin analogs and premixes currently available**

Analog	Trade name/ manufacturer
<b>Rapid-acting analogs</b>	
Lispro	Humalog/Eli Lilly
Aspart	Novolog/Novo Nordisk
Glulisine	Apidra/sanofi-aventis
<b>Long-acting analogs</b>	
Glargine	Lantus/sanofi-aventis
Detemir	Levemir/Novo Nordisk
<b>Premixed analogs</b>	
75% neutral protamine lispro, 25% lispro	75/25 Humalog/Eli Lilly
50% neutral protamine lispro, 50% lispro	50/50 Humalog/Eli Lilly
70% protamine aspart, 30% aspart	70/30 Novolog/Novo Nordisk

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namic characteristics, longer durations of action (up to 24 hours, allowing for once-daily dosing), less risk of hypoglycemia, and more predictable action than NPH insulin.<sup>45,46</sup> Insulin detemir is also associated with less weight gain than NPH insulin.<sup>45</sup> Insulin glargine has been shown to be as effective as bedtime NPH insulin in improving glycemic control, with less nocturnal hypoglycemia.<sup>47-49</sup> Insulin detemir has also been shown to be effective as basal insulin therapy in patients with type 2 diabetes and to have lower risk for hypoglycemia than NPH insulin.<sup>50-52</sup>

#### Premixes of insulin analogs

The limitations of human premixed insulins have been addressed by using newer insulin analog premix preparations. Analogs more closely approximate physiologic insulin secretion compared with human premix formulations, which reduces the risk for hypoglycemic episodes and provides more flexibility in dosing.<sup>34</sup> These newer biphasic insulin preparations have been shown to be effective for achieving glycemic control,<sup>53,54</sup> and they may also decrease the risk for hypoglycemia.<sup>55</sup> Specific subgroups of patients may be particularly suited

for treatment with premixes of insulin analogs. These include individuals with consistent mealtimes and lifestyles<sup>31</sup> and those whose adherence to treatment may be enhanced by a simple treatment regimen.<sup>34</sup>

### Benefits and risks/limitations of insulin therapy in patients with type 2 diabetes

Insulin, when properly dosed, is the most potent drug available to achieve tight glycemic control and avoid long-term disease complications.<sup>28</sup> The newer long- and rapid-acting insulin analogs and premixed insulin analogs have time-action profiles that more closely mimic physiologic insulin secretion than do human insulin formulations. These preparations provide

superior flexibility and convenience and thus may improve quality of life for patients.<sup>28</sup> Nevertheless, there are limitations associated with the use of insulin in general. Concern about hypoglycemia is an important barrier to insulin therapy, and weight gain is common among patients receiving insulin;<sup>56</sup> however, weight gain may also occur with some oral antidiabetic agents.<sup>57</sup> Insulin therapy also requires regular and frequent glucose monitoring<sup>58</sup> as well as increased patient involvement in the treatment regimen. Nevertheless, modern insulin treatment regimens are effective and well tolerated,<sup>59</sup> and because of the progressive nature of type 2 diabetes and the inevitable decline in  $\beta$ -cell function, such treatment is needed by most patients to maintain glycemic control.<sup>59</sup> ■

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**STUDY KEY**

**Abbreviations of studies mentioned in this article**

<b>ACCORD</b>	Action to Control Cardiovascular Risk in Diabetes study
<b>ADVANCE</b>	Action in Diabetes and Vascular Disease study
<b>DIGAMI 2</b>	Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study
<b>HEART2D</b>	Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes study
<b>NHANES</b>	National Health and Nutrition Examination Surveys
<b>ORIGIN</b>	Outcome Reduction With Initial Glargine Intervention trial
<b>STOP-NIDDM</b>	Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial
<b>VADT</b>	Veterans Affairs Diabetes Trial
<b>UKPDS</b>	United Kingdom Prospective Diabetes Study