Insulin Therapy and Hypoglycemia

Anthony L. McCall, MD, PhD

KEYWORDS

• Hypoglycemia • Diabetes type 1 • Diabetes type 2
• Insulin therapy

Hypoglycemia impedes safe achievement of optimal glycemia. The benefits of nearly normal glycemia in reducing microvascular diabetes complications are clear, although the benefits and risk-to-benefit ratio for macrovascular disease is contentious and complex. Overall achievement of excellent glycemia seems beneficial to cardiovascular risk when implemented early in the course of both type 1 and type 2 diabetes. Despite strong evidence of likely benefit, those trying to decrease the risk of microvascular complications through intensive glycemic control inevitably face a 3-fold increased risk of severe hypoglycemia, often without warning symptoms and potentially with severe consequences, especially to heart and brain. This is especially true for those with type 1 diabetes mellitus (DM) but also for insulin-deficient patients with type 2 DM (**Fig. 1**).

Studies of glycemic control and diabetes complications before ACCORD (Action to Control Cardiovascular Risk in Diabetes),[1] ADVANCE (Action in Diabetes to Prevent Vascular Disease),[2] and VADT (Veterans Administration Diabetes Trial)[3] indicate that severe hypoglycemia is less common with tight glycemic control in type 2 (see **Fig. 1**, left) when compared with type 1 DM (see **Fig. 1**, right). Studies of type 1, such as the DCCT (Diabetes Control and Complications Trial), show that severe insulin reactions occur up to severalfold more than 60 per 100 patient-years and have a threefold increased risk relative to those of control groups with less intensive glucose control. Studies of type 2 diabetes, by contrast, found a risk of severe hypoglycemia with tight glycemic control that was substantially less. It is noteworthy, however, that some studies found an overlap in frequency indicating that some type 2 DM[4–12] patients have a risk comparable with that seen with intensive control in type 1 DM.[13–18]

Optimal glycemia goals must be individualized, but may be generally defined as hemoglobin A_{1c} ($HgbA_{1c}$) of less than 7% (**Table 1**) as recommended by the American Diabetes Association (ADA).[19] A simplified summary is to achieve the best possible control by trying to achieve control that is as tight as possible, as early as possible, as safely as possible, for as long as possible. This goal and this strategy are based

Division of Endocrinology, University of Virginia School of Medicine, 450 Ray C. Hunt Drive, Charlottesville, VA 22903, USA
E-mail address: alm3j@virginia.edu

Endocrinol Metab Clin N Am 41 (2012) 57–87
doi:10.1016/j.ecl.2012.03.001 **endo.theclinics.com**
0889-8529/12/$ – see front matter

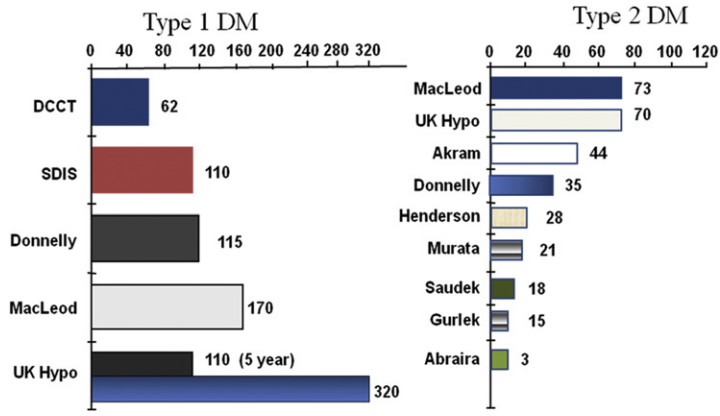

Fig. 1. Severe insulin reactions per 100 patient years.

on evidence from studies in both type 1 and type 2 DM, such as the DCCT and the UKPDS (United Kingdom Prospective Diabetes Study) and their long-term follow-up.[20–22] Moreover, this level of control is more achievable than ever with the panoply of therapies available. Because of negative results from 3 studies of tight control and cardiovascular end points in type 2 diabetes,[1–3] caution is urged in application of tight glycemic control for those with long diabetes duration, advanced complications, or multiple comorbidities. Newer insulins and strategies, such as insulin pumps and continuous glucose monitoring in type 1 DM, and use of drugs combined with insulin that enhances glycemic control for type 2 DM with low hypoglycemia risk, make excellent control usually achievable.

The pathophysiology of hypoglycemia unawareness (inability to recognize hypoglycemia) and defective insulin counterregulation (weakened hormone defenses against hypoglycemia) remains under active investigation. The importance of hypoglycemia as

Table 1
American Diabetes Association 2011 summary of glycemic recommendations for many nonpregnant adults with diabetes

A_{1c}	< 7.0%
Pre-prandial capillary BG	70-130 mg/dl
Peak Post-prandial capillary BG	< 180 mg/dl

Individualization	ALSO
Individualize goals based on: Duration of diabetes Age/life expectancy Comorbid conditions Known cardiovascular disease or advanced microvascular complications Hypoglycemia unawareness Individual patient considerations	More or less stringent glycemic goals may be appropriate for individual patients Postprandial glucose may be despite reaching preprandial glucose goals

Adapted from American Diabetes Association. Standards of medical care in diabetes mellitus. Diabetes Care 2011;34(Suppl 1):S19.