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Glycemic Goals in Diabetes: Trade-off Between Glycemic Control and Iatrogenic Hypoglycemia

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The selection of a glycemic goal in a person with diabetes is a compromise between the documented upside of glycemic control—the partial prevention or delay of microvascular complications—and the documented downside of glycemic control—the recurrent morbidity and potential mortality of iatrogenic hypoglycemia. The latter is not an issue if glycemic control is accomplished with drugs that do not cause hypoglycemia or with substantial weight loss. However, hypoglycemia becomes an issue if glycemic control is accomplished with a sulfonylurea, a glinide, or insulin, particularly in the setting of absolute endogenous insulin deficiency with loss of the normal decrease in circulating insulin and increase in glucagon secretion and attenuation of the sympathoadrenal response as plasma glucose concentrations fall. Then the selection of a glycemic goal should be linked to the risk of hypoglycemia. A reasonable individualized glycemic goal is the lowest A1C that does not cause severe hypoglycemia and preserves awareness of hypoglycemia, preferably with little or no symptomatic or even asymptomatic hypoglycemia, at a given stage in the evolution of the individual's diabetes.

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes (1). It causes recurrent morbidity in most people with type 1 diabetes and many with advanced (absolutely endogenous insulin deficient) type 2 diabetes and is sometimes fatal. It generally precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the benefits of glycemic control. It impairs defenses against subsequent falling plasma glucose concentrations and causes a vicious cycle of recurrent hypoglycemia. The problem of iatrogenic hypoglycemia will be solved by the prevention or cure of diabetes, or the provision of precise insulin replacement or secretion—the former by a closed-loop system or the latter by transplantation of insulin-secreting tissue or β-cell expansion (2). Pending those treatments, we need to better understand the pathophysiology of hypoglycemia-associated autonomic failure (HAAF) in diabetes if we are to lower the barrier of hypoglycemia in diabetes (2).

The concept of HAAF in diabetes posits that iatrogenic hypoglycemia is the result of the interplay of therapeutic hyperinsulinemia, caused by treatment with a sulfonylurea, a glinide, or insulin, and compromised physiologic and behavioral defenses against the resulting falling plasma glucose concentrations (1,2). HAAF includes both defective glucose counterregulation, caused by an attenuated adrenomedullary epinephrine response in the setting of loss of a decrement in circulating insulin and loss of an increment in glucagon secretion, and impaired awareness of hypoglycemia, caused by an attenuated sympathoadrenal, largely sympathetic neural, response. The attenuated adrenomedullary and sympathetic neural responses are most often caused by recent antecedent hypoglycemia (1,2).

The practice of hypoglycemia risk reduction in people with diabetes at risk for iatrogenic hypoglycemia includes *1*) acknowledging the problem, *2*) applying the principles of aggressive glycemic therapy, *3*) considering the conventional risk factors, and *4*) considering the risk factors indicative of HAAF (1). The conventional risk factors include insulin or insulin secretagogue doses that are excessive,

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ill-timed, or of the wrong type; decreased exogenous glucose delivery (as following missed meals and during the overnight fast); decreased endogenous glucose production (as following alcohol ingestion); increased glucose utilization (as during and shortly after exercise); increased sensitivity to insulin (as in the middle of the night and after weight loss or improved glycemic control); and decreased clearance of insulin (as in renal failure). The risk factors indicative of HAAF include the degree of absolute endogenous insulin deficiency (in part a function of the duration of diabetes); a history of severe hypoglycemia, hypoglycemia unawareness, or both as well as an association with recent antecedent hypoglycemia, sleep, or prior exercise; and aggressive glycemic therapy per se.

The selection of a given glycemic goal, such as an A1C of <7.0% (53 mmol/mol) in nonpregnant adults with diabetes recommended by the American Diabetes Association (3), is a compromise between the upside of glycemic control on the one hand, and the downside of glycemic control on the other hand. What is the upside and what is the downside?

UPSIDE OF GLYCEMIC CONTROL: REDUCED MICROVASCULAR COMPLICATIONS

There is convincing evidence from randomized controlled trials that intensive glycemic therapy compared with less intensive (conventional, standard) glycemic therapy partially prevents or delays the microvascular complications (retinopathy, nephropathy, and neuropathy) of type 1 (4) and type 2 (5–11) diabetes.

Intensive glycemic therapy with a mean A1C of approximately 7.2% (55 mmol/mol) compared with conventional glycemic therapy with a mean A1C of approximately 9.1% (76 mmol/mol) partially prevented or delayed the development and progression of retinopathy, development of proliferative or severe nonproliferative retinopathy, development of microalbuminuria and macroalbuminuria, and development of clinical neuropathy in type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) (4). Intensive glycemic therapy with an average mean A1C of 6.9% (52 mmol/mol) compared with conventional therapy with an average mean A1C of 8.0% (64 mmol/mol) partially prevented or delayed aspects of microvascular complications in four of five randomized controlled trials in type 2 diabetes (5–12). Intensive glycemic therapy reduced a composite of microvascular complications, the progression of retinopathy, the development of microalbuminuria and proteinuria, and the doubling of plasma creatinine in the UK Prospective Diabetes Study (UKPDS) (5,6). It reduced the development and progression of retinopathy and nephropathy and improved nerve conduction in the Kumamoto Study (7). It reduced progression of retinopathy, development of microalbuminuria and macroalbuminuria, and loss of light touch in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (8–10). It reduced a composite of major microvascular events and reduced new or worsening nephropathy in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study (11). In contrast, intensive glycemic therapy did not reduce microvascular end points in the smaller Veterans Affairs Diabetes Trial (VADT) (12).

Unfortunately, the effect of intensive glycemic therapy to prevent or delay the microvascular complications of diabetes is partial. Microvascular complications developed in both intensive and conventional glycemic therapy patients, but generally at lower rates in the former (4–11). In addition, the magnitude or partial prevention or delay of microvascular complications appear to have been greater in type 1 diabetic patients (4) than in type 2 diabetic patients (5–11), perhaps because of the generally lower A1C levels in the less intensively treated type 2 diabetic patients (5–11) compared with that in the less intensively treated type 1 diabetic patients (4) (i.e., due to a smaller difference in glycemic control between the two groups in the type 2 diabetes series).

On the other hand, there is not convincing evidence from these or other randomized controlled trials that intensive glycemic therapy prevents or delays the key outcome of macrovascular complications, cardiovascular mortality, in type 1 diabetes (4) or type 2 diabetes (5–14). Aside from the main metformin subset of UKPDS, in which there was reduced all-cause and cardiovascular mortality (6)—although both all-cause and cardiovascular mortality were increased in the subset in whom metformin was added to a sulfonylurea—the major evidence that intensive glycemic therapy partially prevents or delays the key macrovascular complications of diabetes is limited to epidemiologic studies, including follow-up of DCCT patients (the DCCT/Epidemiology of Diabetes Interventions and Complications [EDIC] study) with type 1 diabetes (15) and of the UKPDS patients with type 2 diabetes (16). In DCCT/EDIC, former intensive glycemic therapy was associated with a decreased risk of any cardiovascular event (15). In the UKPDS follow-up, former intensive glycemic therapy was associated with reduced myocardial infarction and all-cause mortality in type 2 diabetes (16).

Meta-analyses of these and other randomized controlled trials have indicated that intensive glycemic therapy reduced cardiac and peripheral macrovascular events in type 1 diabetes (17) and stroke and peripheral macrovascular events in type 2 diabetes (17), as well as nonfatal myocardial infarction in type 2 diabetes (18,19). Nonetheless, none of these meta-analyses indicated that intensive glycemic therapy reduced the key outcome of macrovascular disease, cardiovascular mortality, in type 1 (17) or type 2 (18–20) diabetes (Table 1). Meta-analysis further indicated that intensive glycemic therapy partially prevented or delayed microvascular complications, albeit to a rather small degree, and increased the rate of hypoglycemia more substantially in type 2 diabetes (20) (Table 1). Intensive therapy also increased the rate of hypoglycemia in type 1 diabetes (4). Again, aside from the main metformin subset of the UKPDS (6), the major evidence that

Table 1—Effects of intensive, compared with conventional, glycemic therapy of type 2 diabetes: meta-analysis of 12 randomized controlled trials (20)

Effect (no. of randomized controlled trials)	Relative risk	95% CI (*P*)	No. of patients
All-cause mortality (12)	1.02	0.91–1.13 (0.74)	28,359
Cardiovascular mortality (12)	1.11	0.92–1.35 (0.27)	28,359
Microvascular complications (3)	0.88	0.79–0.97 (0.01)	25,600
Severe hypoglycemia (9)	2.39	1.71–3.34 (0.001)	27,844

intensive glycemic therapy reduces the key outcome of the macrovascular complications of diabetes is limited to epidemiologic studies, including follow-up of the DCCT/EDIC (15) and UKPDS (16) patients.

Prevention of macrovascular complications was not demonstrated in the randomized controlled DCCT (4) and UKPDS (5,6) trials. Indeed, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial data (21,22) do not support the conclusion that tight glycemic control reduces cardiovascular outcomes in diabetes. In ORIGIN, patients with type 2 diabetes (or a minority with impaired fasting glucose or impaired glucose tolerance), all with high cardiovascular risk, were randomized to evening insulin glargine administration in doses designed to lower fasting plasma glucose concentrations to <5.3 mmol/L (95 mg/dL), i.e., to normalize fasting glucose (n = 6,264), or to conventional glycemic management (n = 6,273). After 6.2 years of follow-up, with a median fasting plasma glucose of 5.2 mmol/L (94 mg/dL) and A1C of 6.2% (44 mmol/mol), there was no reduction in cardiovascular outcomes in the glargine group (21). On the other hand, the subset of ORIGIN patients, mostly in the glargine group, who suffered severe hypoglycemia—requiring the assistance of another person or having a plasma glucose concentration ≤2.0 mmol/L (36 mg/dL)—were at significantly increased risk of cardiovascular, all-cause, and arrhythmic mortalities and a composite of cardiovascular death or nonfatal myocardial infarction or nonfatal stroke (22) (Table 2). Thus, normalization of fasting glucose for more than 6 years in more than 6,000 patients did not reduce cardiovascular outcomes, but severe iatrogenic hypoglycemia increased cardiovascular outcomes. From the perspective of acute cardiovascular events, the net effect of tight glycemic control with insulin in diabetes in ORIGIN was harm. However, it is conceivable that ORIGIN was too short to demonstrate an effect of glycemic control to significantly interrupt the pathogenesis of atherosclerotic macrovascular disease (23). It remains to be seen if early and sustained glycemic control does so.

DOWNSIDE OF GLYCEMIC CONTROL: HYPOGLYCEMIC MORBIDITY AND MORTALITY

Thus, partial prevention or delay of the microvascular complications of diabetes is the documented upside of intensive glycemic therapy of diabetes. But, the morbidity and potential mortality of hypoglycemia are the documented downside of intensive glycemic therapy of diabetes with insulin, a sulfonylurea, or a glinide (1,4–12,20).

An episode of hypoglycemia is, at best, a nuisance. Hypoglycemia can cause embarrassment, social ostracism, and employment discrimination as well as aberrant behaviors, anxiety, and impairment of physical performance. It often involves unpleasant symptoms such as palpitations, tremulousness, sweating, and hunger as well as neuroglycopenia ranging from impaired cognition and confusion to seizure and coma. Injuries or permanent neurological deficits sometimes occur. The most devastating downside, of course, is hypoglycemic death.

Despite some exceptions (24,25), there is abundant evidence that iatrogenic hypoglycemia, caused by treatment of diabetes with insulin or a sulfonylurea (or theoretically a glinide), is associated with death of people with diabetes (26,27). Obviously, hypoglycemia is not the cause of death that occurs in the absence of hypoglycemia. Furthermore, as there are other causes of hypoglycemia, including critical illnesses (28), all hypoglycemia is not iatrogenic hypoglycemia. Finally, an epidemiologic association between the occurrence of hypoglycemia and death in a population does not establish that hypoglycemia was the cause of all, or even any, of the deaths.

There is no doubt that iatrogenic hypoglycemia can kill. The Toronto investigators' insulin extract sometimes killed diabetic dogs, and those investigators in 1922 found that convulsions and death following insulin extract

Table 2—Cardiovascular outcomes in the ORIGIN trial (21,22): effect of normalization of fasting plasma glucose and A1C by evening insulin glargine administration

Groups	Outcomes	Hazard ratio (95% CI)	*P*
Insulin glargine vs. standard care	Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	1.02 (0.94–1.11)	0.63
Subset with severe hypoglycemia	Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	1.58 (1.24–2.02)	<0.001
	Total mortality	1.74 (1.39–2.19)	<0.001
	Cardiovascular death	1.71 (1.27–2.30)	<0.001
	Arrhythmic death	1.77 (1.17–2.67)	<0.001

administration to rabbits were associated with low blood glucose concentrations and could be prevented by intravenous glucose administration (29). Deaths of patients with diabetes from "insulin reactions" were reported in 1923 (29). Deaths during or shortly after insulin coma therapy for psychiatric disorders were reported in 1952 (30). In addition, high mortality rates characterize experimental hypoglycemia (31–33).

In large randomized controlled trials in intensive care unit patients—the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) (34,35) and Control of Hyperglycaemia in Paediatric Intensive Care (CHiP) (36) studies—intensive glucose-lowering with insulin was associated with increased hypoglycemia and increased mortality. Death was more associated with hypoglycemia than with intensive glycemic therapy per se (34–36). These data do not document that increased hypoglycemia was a cause of excessive mortality, but they are consistent with that interpretation.

Older estimates were that 2–4% of patients with type 1 diabetes die of iatrogenic hypoglycemia (37–39). More recent estimates are that 4% (40), 6% (41), 7% (42), or 10% (43) of those with type 1 diabetes die of hypoglycemia. In the judgment of the reporting physicians, these deaths were caused by iatrogenic hypoglycemia. A causal connection between therapeutic insulin-induced hypoglycemia and death was further supported by continuous glucose monitoring data in a patient with type 1 diabetes found dead in bed (44). After insulin administration before he retired, his subcutaneous glucose concentrations fell progressively to 0.6 mmol/L (10 mg/dL) during the night before he was found dead the following morning. Thus, the patient must have been profoundly hypoglycemic at the time of death. Notably, McCoy et al. (45) reported 3.4-fold higher mortality, without a difference in Charlson comorbidity indices, in patients with type 1 or type 2 diabetes who self-reported severe hypoglycemia (that requiring the assistance of another person) 5 years earlier. Thus, whatever the precise rate, there is an iatrogenic hypoglycemia mortality rate in type 1 diabetes.

Iatrogenic hypoglycemia, typically prolonged and profound hypoglycemia, can cause brain death, but hypoglycemic mortality is most often the result of a cardiac arrhythmia triggered by a sympathoadrenal discharge during an episode of hypoglycemia (1,26,27,33). Indeed, reduced baroreflex sensitivity, which increases the risk of a fatal arrhythmia, is a feature of HAAF (1,25,26,46). An association between insulin-induced hypoglycemia and acute cardiovascular events has been recognized (47,48), and a patient with hypoglycemia who developed ventricular tachycardia that reverted to sinus rhythm after intravenous glucose administration has been reported (49).

Deaths have also been attributed to hypoglycemia caused by treatment of type 2 diabetes with a sulfonylurea (50–52). Again, the reporting physicians believed these deaths were caused by iatrogenic hypoglycemia. Case fatality rates in sulfonylurea-induced hypoglycemia have ranged as high as 10% (52). In addition, higher mortality rates have been reported in sulfonylurea-treated compared with metformin-treated type 2 diabetes (53,54). There were also associations between iatrogenic hypoglycemia and mortality in more recent randomized controlled trials of intensive glycemic therapy that included treatment of type 2 diabetes with insulin in many instances (8,11,14). In one of those trials, the ACCORD trial, there was both increased hypoglycemia and excessive mortality in the intensive glycemic therapy group (8). That excessive mortality could have been the result of chance, a nonglycemic effect of the intensive therapy regimen, or hypoglycemia. As plasma glucose concentrations at the time of the deaths are not known, we do not know with certainty whether hypoglycemia was or was not a cause of the excessive deaths. In a random-sample cohort epidemiologic study of patients with type 2 diabetes, symptomatic hypoglycemia, whether clinically mild or severe, was found to be associated with increased mortality (55). In another cohort study, involving hospitalized patients, mortality of insulin-treated hypoglycemic patients was 4.5-fold higher than that of insulin-treated nonhypoglycemic control patients (56), while the Charlson comorbidity indices were similar in the two groups. Mortality in the smaller number of noninsulin-treated hypoglycemic patients was 31-fold higher than that of noninsulin-treated nonhypoglycemic control patients. Notably, the Charlson comorbidity index in the hypoglycemic patients was more than twice that in the nonhypoglycemic patients. The latter finding, which is identifiable in several other reports, raises an important point. Clearly, hypoglycemia occurs in nondiabetic patients as well as diabetic patients with critical illnesses (28) and may be a marker of illness or a cause of death. Notably, a meta-analysis and bias analysis of cohort studies of patients with type 2 diabetes indicated that a history of severe hypoglycemia doubled the risk of cardiovascular disease and concluded that comorbid severe illness was not likely to explain that association (57). Again, more than 6 years of normalization of fasting glucose in more than 6,000 patients did not reduce cardiovascular outcomes in type 2 diabetes (21) and cardiovascular outcomes were increased in the subset of patients who suffered severe iatrogenic hypoglycemia (22).

Finally, an association between low (as well as high) A1C levels and mortality in patients with diabetes has been documented in several reports (58–62). Again, this could be a marker of impending death, a predictor of the cause of impending death, or both.

Thus, while partial prevention or delay of microvascular complications is the upside of intensive therapy in diabetes, the morbidity and potential mortality of iatrogenic hypoglycemia is the downside of intensive glycemic therapy in diabetes.

SUMMARY OF THE EVIDENCE AND THERAPEUTIC IMPLICATIONS

The evidence that glycemic control partially prevents or delays microvascular complications in both type 1 and

type 2 diabetes is compelling (4–11). It provides a convincing rationale for tight glycemic control and against loose glycemic control. While not excluded categorically by available data, the evidence that glycemic control partially prevents or delays macrovascular complications in type 1 and type 2 diabetes (15,16) is not compelling (4–11,17–22). Therefore, it does not provide a convincing rationale for tight glycemic control. The evidence that glycemic control with insulin, a sulfonylurea, or a glinide increases hypoglycemic morbidity and mortality in type 1 and type 2 diabetes is compelling (22,36–45,47–62). Unless tight glycemic control empirically can be achieved and maintained safely, the evidence provides a convincing rationale against tight glycemic control, but not for loose glycemic control, during treatment with those drugs. This issue does not apply if glycemic control is pursued with drugs that do not cause hypoglycemia or follows substantial lifestyle, medical, or surgical weight loss.

GLYCEMIC GOALS LINKED TO HYPOGLYCEMIA RISK

While generally endorsing a glycemic goal of an A1C <7.0% (53 mmol/mol) in most nonpregnant adults, a joint American Diabetes Association/European Association for the Study of Diabetes group has advocated more flexibility in the selection of a glycemic goal in an individual with diabetes (63). They suggested that a more stringent glycemic goal might be selected in a person with a short duration of diabetes, a long life expectancy, and no significant cardiovascular disease if that could be achieved without significant hypoglycemia or other adverse effects of treatment. Alternatively, they suggested that a less stringent glycemic goal might be selected in a person in whom the target is difficult to maintain or with a history of severe hypoglycemia, long-standing diabetes, advanced complications, extensive comorbid conditions, and limited life expectancy. In my view, these recommendations are unnecessarily broad. In a patient in whom maintenance of an A1C of <7.0% (53 mmol/mol) without severe hypoglycemia and without loss of awareness of hypoglycemia is empirically possible, should one abandon that goal because the patient has had diabetes for 20, 30, 40, or 50 years; has a history of treated proliferative retinopathy or a renal transplant; or has one or more other chronic illnesses? I think not. I submit that the selection of a glycemic goal should be linked to the risk of iatrogenic hypoglycemia (Fig. 1).

One assumption central to such recommendations about the selection of a glycemic goal for an insulin- or sulfonylurea-treated person with diabetes (3,63) is that a lower A1C level is associated with an increased risk of iatrogenic hypoglycemia. Clearly, iatrogenic hypoglycemia can occur in patients with relatively high A1C values. Nonetheless, a consistent finding in randomized controlled clinical trials that include a control group—patients treated to a higher A1C—and an experimental group—patients treated to a lower A1C—is a higher incidence of hypoglycemia in those treated to a lower A1C in both type 1 diabetes (4) and type 2 diabetes (5,7,8,11,12). Thus, a low A1C is a risk factor for iatrogenic hypoglycemia (1). That fact is not refuted by studies lacking a control group, particularly those of patients with a narrow range of A1C values.

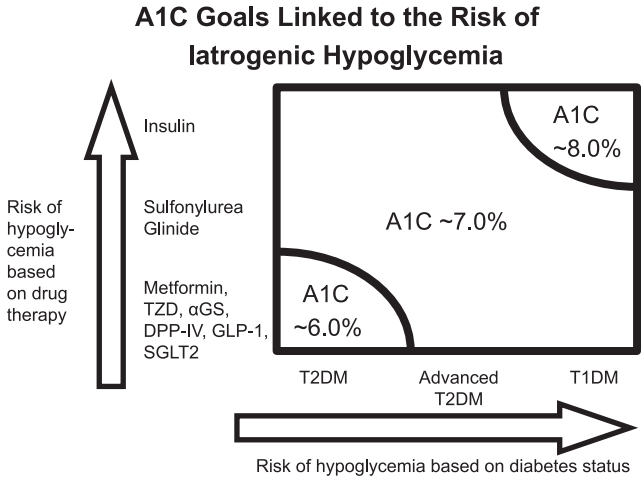

Figure 1—Concept of A1C goals linked to the risk of iatrogenic hypoglycemia in diabetes based on drug therapy and diabetes status. Treatment with a sulfonylurea, a glinide, or insulin and greater absolute endogenous insulin deficiency increase the risk of hypoglycemia. αGS, α-glycosidase inhibitors; advanced T2DM, absolutely endogenous insulin-deficient type 2 diabetes mellitus; DPP-IV, dipeptidyl peptidase inhibitors; GLP-1, glucagon-like peptide 1 receptor agonists; SGLT2, sodium-glucose transporter 2 inhibitors; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TZD, thiazolidinediones.

As the trade-off in the selection of a glycemic goal in a given patient with diabetes is between the documented upside of glycemic control—partial prevention or delay of the microvascular complications of diabetes—and the documented downside of glycemic control—the morbidity and potential mortality of increased iatrogenic hypoglycemia—it would seem that the risk of hypoglycemia should be the focus of the selection of the glycemic goal (Fig. 1). A reasonable individualized glycemic goal is the lowest A1C that does not cause severe hypoglycemia (that requiring the assistance of another person [1]) and preserves awareness of hypoglycemia (suggesting the absence of recent antecedent hypoglycemia [1,2]), preferably with little or no symptomatic or even asymptomatic hypoglycemia at a given stage in the evolution of the individual's diabetes (1,26). Even an episode of severe hypoglycemia with a history of hypoglycemia unawareness, which dictates some action (1), might not force an immediate higher glycemic goal until one has tried patient reeducation (1,64) and a 2–3 week trial of scrupulous avoidance of hypoglycemia (1,65–68) with the anticipation that these might reverse hypoglycemia unawareness and reduce the risk of severe hypoglycemia.

During effective intensive therapy of early type 2 diabetes with lifestyle changes or drugs that should not,

and probably do not (1), cause hypoglycemia (i.e., drugs other than a sulfonylurea, a glinide, or insulin among currently available glucose-lowering medications), a reasonable glycemic goal might be a normal A1C (Fig. 1). That could be successful without hypoglycemia if one did not use a sulfonylurea (or a glinide) or insulin (69) and could be beneficial over a substantial portion of the course of type 2 diabetes. But, noninsulin therapies are seldom successful over a lifetime of type 2 diabetes and are not effective in type 1 diabetes. During therapy of type 2 diabetes with a sulfonylurea or even insulin early on (70) or of type 1 diabetes with insulin very early on (70), the appropriate glycemic goal might be an A1C of <7.0% (53 mmol/mol) (3) if that can be achieved and maintained safely—without severe hypoglycemia, without hypoglycemia unawareness, and without excessive symptomatic or asymptomatic hypoglycemia (Fig. 1). However, the added potential harm of iatrogenic hypoglycemia dictates consideration of a somewhat higher A1C (Fig. 1). If an A1C of <7.0% (53 mmol/mol) is not achievable safely, there is demonstrable microvascular benefit from reducing A1C from high to lower, albeit still above ideal, levels (71). Indeed, the relationship between A1C and microvascular complications is curvilinear and that curve becomes progressively more flat as A1C is reduced toward 7.0% (53 mmol/mol) (4,71). Finally, if life expectancy is clearly known to be too limited for conceivable benefit from glycemic control, glucose levels low enough to prevent symptoms of hyperglycemia become a reasonable glycemic goal.

CONCLUSIONS

The selection of a glycemic goal for a given patient at a given point in the evolution of that individual's diabetes is a compromise. While partial prevention or delay of microvascular complications is the upside, the morbidity and potential mortality of iatrogenic hypoglycemia are the downside of intensive glycemic therapy in diabetes. A reasonable individualized glycemic goal is the lowest A1C that does not cause severe hypoglycemia and preserves awareness of hypoglycemia, preferably with little or no symptomatic or even asymptomatic hypoglycemia. The selection of a glycemic goal should be linked to the risk of hypoglycemia, lower in those treated with weight loss or drugs that do not cause hypoglycemia and higher in those treated with a sulfonylurea, a glinide, or insulin.

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