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Journal of Diabetes and Its Complications 25 (2011) 202–207

Journal of Diabetes and its Complications

WWW.JDCJOURNAL.COM

The importance of glycemic control: how low should we go with HbA1c? Start early, go safe, go low☆

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Received 12 January 2010; received in revised form 15 March 2010; accepted 29 March 2010

Abstract

Epidemiologic data indicate a continuous relationship between hemoglobin A1c (HbA1c) and risk for microvascular and macrovascular complications of diabetes. Intensive glycemic control reduces risk of microvascular complications in Type 1 and Type 2 diabetes, and long-term treatment and follow-up studies have shown that initial intensive control is associated with reduced cardiovascular risk. Recent intervention trials in older, high-risk patients with Type 2 diabetes have not shown a benefit of intensive control in reducing cardiovascular risk over a rather short-term follow-up period of up to 5 years, with some data indicating that intensive control accompanied by hypoglycemia is detrimental in patients with high cardiovascular risk. Indeed, hypoglycemia with current antidiabetic agents—primarily insulin and sulphonylureas—is the main limiting factor in achieving desirable levels of glycemic control. Still, the goal in treating both Type 1 and Type 2 diabetes should be to safely get HbA1c as close to normal as possible. In Type 2 diabetes, this goal should be tempered for the time being in patients with shorter life expectancy or co-existing cardiovascular disease or other co-morbidities, in whom a target of 7.0–7.5% may be advisable until we can demonstrate that lower targets in such patients can be safely achieved. Newer agents with lower risk of hypoglycemia—e.g., insulin analogues, incretin mimetics and incretin enhancers—may form an integral component of strategies for safely achieving lower HbA1c levels.

Keywords: Diabetes; Hypoglycemia; HbA1c; Microvascular complications; Cardiovascular complications

1. Introduction

Patients with diabetes are at increased risk of microvascular complications and cardiovascular disease compared with the general population. Compared to those with Type 2 diabetes, patients with Type 1 diabetes have lower rates of such risk factors as obesity, hypertension, and dyslipidemia, and their elevated lifetime cardiovascular risk appears to be more directly related to hyperglycemia. Cardiovascular risk in patients with Type 2 diabetes reflects both the effects of hyperglycemia and a high frequency of such additional risk factors. Available evidence indicates that any increase in hemoglobin A1c (HbA1c) above normal levels is associated with increased risk of microvascular and cardiovascular complications (Fig. 1) (Khaw et al., 2004; Krzentowski, Zhang, Albert, & Lefèbvre, 2004; Stratton et al., 2000), providing the rationale for treatment to reduce glucose to normal or near-normal levels. Initial trials of intensive glycemic control showed benefits in reducing microvascular complications in both Type 1 (The Diabetes Control and Complications Trial Research Group, 1993) and Type 2 diabetes (UK Prospective Diabetes Study (UKPDS) Group, 1998a, 1998b), with inconclusive evidence regarding prevention of cardiovascular events. Three recently reported

☆ Conflicts of interests/disclosures: Dr. Benhalima has no conflicts of interest. Dr. Standl has been an advisor/lecturer/investigator for activities sponsored by Astra-Zeneca, Bayer-Schering, BMS, Johnson & Johnson, Merck, MSD, Novartis and Novo Nordisk. Dr. Mathieu is/has been advisor for Eli Lilly, Merck, Sharp & Dohme, Novartis, Novo Nordisk and Sanofi Aventis. Editorial assistance provided by BioScience Communications.

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1056-8727/$ – see front matter © 2011 Published by Elsevier Inc.
doi:10.1016/j.jdiacomp.2010.03.002

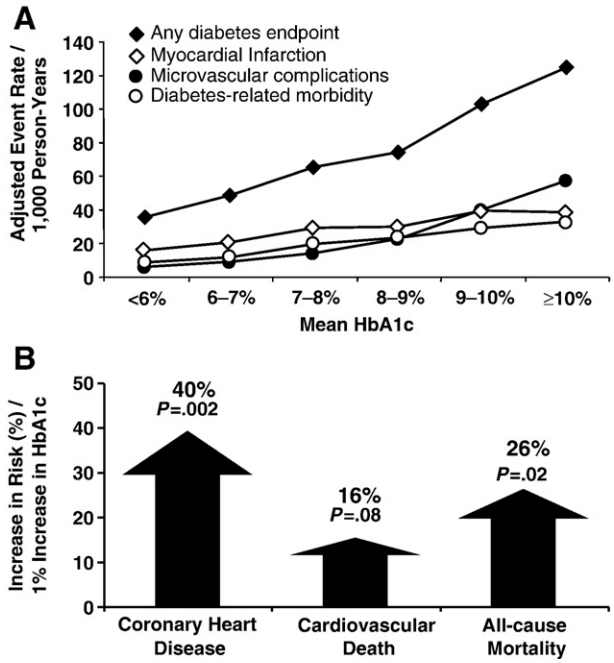

Fig. 1. (A) Relationship between updated mean HbA1c and risk for diabetic complications in patients with newly diagnosed Type 2 diabetes in the prospective observational UKPDS-35 study. Each 1% decrease in mean HbA1c was associated with risk reductions of 21% for any diabetes endpoint ($P<.0001$), 21% for diabetes-related mortality ($P<0.0001$), 14% for myocardial infarction (MI) ($P<.0001$) and 37% for microvascular complications ($P<.0001$) (Stratton et al., 2000). (B) Association between a 1% increase in HbA1c and risk for coronary heart disease, cardiovascular death and all-cause mortality among more than 10,000 men and women aged 45–79 years from the general population in the European Prospective Investigation into Cancer in Norfolk study (Khaw et al., 2004).

trials in Type 2 diabetic patients showed no benefit of intensive control in reducing cardiovascular risk over the short term (The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008; The ADVANCE Collaborative Group, 2008; Duckworth et al., 2009), whereas long-term follow-up studies over 17 years and longer both in Type 1 (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, 2005) and Type 2 diabetes (Holman, Paul, Bethel, Matthews, & Neil, 2008) showed significant reductions in cardiovascular risk in patients who had received intensive therapy. When all of these findings are incorporated into the debate over how low we should go with HbA1c, the conclusion that still beckons is that we should go as low as we safely can.

2. HbA1c reduction in Type 1 diabetes

The Diabetes Control and Complications Trial (DCCT), reported in 1993, demonstrated that intensive glycemic control in patients with newly diagnosed Type 1 diabetes produced a dramatic reduction in risk for microvascular complications—including retinopathy, nephropathy, and neuropathy—compared with conventional insulin treatment over 6.5 years of follow-up (The Diabetes Control and Complications Trial Research Group, 1993). For example, intensive control significantly reduced risk of retinopathy by 76% in the primary prevention cohort; risk of retinopathy progression and development of proliferative or severe non-proliferative retinopathy decreased by 54% and 47%, respectively, in the secondary prevention cohort. For both treatment groups in the study, there was no HbA1c threshold for risk of retinopathy (The Diabetes Control and Complications Trial Research Group, 1996).

There were few macrovascular events in the DCCT trial, limiting the ability to generate conclusions regarding preventive benefit. When all major cardiovascular and peripheral vascular end points were combined, intensive control was associated with a nonsignificant 41% reduction in risk for macrovascular disease during the study period. However, the significant benefit of this initial period of intensive control in reducing cardiovascular risk emerged over long-term follow-up in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, 2005). After 11 years of follow-up, subsequent to the conclusion of the initial study (approximately 17 years total), during which time the difference in HbA1c between the initial intensive control and conventional control groups decreased to 0.2%, and the intensive control group had a significant 42% reduction in risk for any cardiovascular disease ($P=.02$) and a 57% reduction in risk for nonfatal myocardial infarction, stroke, or cardiovascular mortality ($P=.02$). On risk factor analysis, this risk reduction was primarily associated with the reduction in HbA1c during DCCT trial treatment; although microalbuminuria and albuminuria were associated with increased risk for cardiovascular disease, the association between the initial HbA1c reduction and reduction in cardiovascular risk remained significant after adjustment for these factors.

3. HbA1c reduction in Type 2 diabetes

As shown in Fig. 1, the prospective observational UKPDS-35 study demonstrated a continuous relationship between HbA1c and microvascular and macrovascular risk among patients with newly diagnosed Type 2 diabetes. An epidemiological extrapolation of this study showed that each 1% reduction in mean updated HbA1c was associated with significant decreases in risk for any diabetes end point, diabetes-related mortality, myocardial infarction, and microvascular complications, with no threshold of risk being observed for any end point (Stratton et al., 2000). Risk for complications is shown by HbA1c strata of <6%, 6–<7%