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What Should the Hemoglobin A_{1c} Level Goal be in Diabetics?

Review Article

Aronow WS

Professor of Medicine, Cardiology Division, Department of Medicine, Westchester Medical Center/New York Medical College, Valhalla, NY, USA.

Abstract

An increased hemoglobin A_{1c} level in patients with diabetes mellitus is associated with an increased incidence of ischemic stroke, increased severity of coronary artery disease, and an increased severity of peripheral arterial disease. Results from 5 prospective clinical trials which randomized diabetics to intensive blood glucose control or to standard blood glucose control and one retrospective observational study of 26,673 diabetics are discussed. The 5 clinical trials were the United Kingdom Prospective Diabetes Study, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Study, the Action to Control Cardiovascular Risk in Diabetes Study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modifies-Release Controlled Evaluation Study, and the Veterans Affairs Diabetes Trial. Severe hypoglycemia may be associated with cardiovascular events and mortality. Recommendations from the 2007 scientific statement from the American Heart Association and the American Diabetes Association, the 2011 American Heart Association/American College of Cardiology Foundation secondary prevention guidelines in patients with coronary and other atherosclerotic vascular disease, the 2013 American Diabetes Association guidelines, and the 2013 American Geriatrics Society guidelines for improving the care of older adults with diabetes mellitus are also discussed.

Keywords: Diabetes Mellitus; Hemoglobin A_{1c}; Macrovascular Disease; Microvascular Disease; Hypoglycemia.

***Corresponding Author**:
Wilbert S. Aronow MD, FACC, FAHA,
Professor of Medicine, Cardiology Division, New York Medical College,
Macy Pavilion, Room 141, Valhalla, NY 10595, USA.
Tel: (914) 493-5311
Fax: (914) 235-6274
E-mail: wsaronow@aol.com

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An increased hemoglobin A_{1c} level in patients with diabetes mellitus is associated with an increased incidence of ischemic stroke [1], with an increased severity of coronary artery disease [2], and with an increased severity of peripheral arterial disease [3]. This article will discuss the results from the randomized clinical trials on what the hemoglobin A_{1c} level should be in patients with diabetes mellitus and the recommendations from recent guidelines on what the hemoglobin A_{1c} level should be in patients with diabetes mellitus.

The United Kingdom Prospective Diabetes Study randomized 3,867 patients, mean age 53 years, with Type 2 diabetes mellitus to intensive blood sugar control versus standard blood sugar control [4]. The hemoglobin A_{1c} level over a 10-year period was 7.0% in the intensive blood sugar control group versus 7.9% in the standard blood sugar control group. This randomized clinical trial demonstrated a significant 25% risk reduction in microvascular endpoints and an insignificant 16% reduction in myocardial infarction with a hemoglobin A_{1c} level of 7.0% [4].

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Study randomized 1,394 patients, mean age 27 years, with Type 1 diabetes mellitus and no clinical cardiovascular disease, hypertension, or hypercholesterolemia to intensive or standard blood sugar control with insulin [5]. The hemoglobin A_{1c} level was 7.4% in the intensive blood sugar control group versus 9.1% in the standard blood sugar control group. At 17-year follow-up, there was a significant 57% reduction in the risk of a first occurrence of a myocardial infarction, stroke, or cardiovascular death in the group with a hemoglobin A_{1c} level of 7.4% [5].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group randomized 10, 251 patients, mean age 62.2 years, with Type 2 diabetes mellitus and cardiovascular disease or additional cardiovascular risk factors to receive intensive blood sugar control or standard blood sugar control [6]. The hemoglobin A_{1c} level was 6.4% in the intensive blood sugar control group versus 7.5% in the standard blood sugar control group. At 3.5-year mean follow-up, the primary outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes was not significantly different between both treatment groups [6]. The hemoglobin A_{1c} 6.4% group had a significant 24% reduction in nonfatal myocardial infarction but a 35% significant increase in cardiovascular death and a significant 22% increase in all-cause mortality which caused termination of intensive blood sugar control in this study [6]. At 5-year follow-up

from randomization, all-cause mortality was still significantly increased 19% [7]. Hypoglycemia requiring medical assistance occurred in significantly more patients treated with intensive glucose control treatment (10.5%) than in patients treated with standard glucose control treatment (3.5%) [6]. It is plausible that the excess mortality in the hemoglobin A_{1c} 6.4% group was due to serious hypoglycemia [8]. Acute hypogycemia has been shown to reduce myocardial blood flow reserve in patients with Type 1 diabetes mellitus [9].

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modifies-Release Controlled Evaluation (ADVANCE) Study randomized 11,140 patients, mean age 66 years, with Type 2 diabetes mellitus and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease to receive intensive blood sugar control or standard blood sugar control [10]. The hemoglobin A_{1c} level was 6.5% in the intensive blood sugar control group versus 7.3% in the standard blood sugar control group at 5-year median follow-up [10]. At 5-year median follow-up, the incidence of death from cardiovascular causes, all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke was similar in both treatment groups [10]. However, intensive blood glucose control significantly reduced new or worsening nephropathy or retinopathy 14%, primarily because of a significant 21% reduction in the incidence of nephropathy from 5.2% to 4.1% in the group with a hemoglobin A_{1c} level of 6.5% [10]. Severe hypoglycemia was significantly increased 86% from 1.5% to 2.7% in the group with a hemoglobin A_{1c} level of 6.5% [10]. At a post-trial follow-up of 5.4 years in the glucose treatment groups in the ADVANCE study, there was no difference in the incidence of major macrovascular events or all-cause mortality between both treatment groups [11]. In the ADVANCE trial, severe hypoglycemia significantly increased the risk of major macrovascular events 288%, major microvascular events 81%, cardiovascular death 268%, and all-cause mortality 269% [12].

The Veterans Affairs Diabetes Trial (VADT) randomized 1,791 patients (97% men), mean age 60.4 years, with Type 2 diabetes mellitus to intensive blood glucose control with a hemoglobin A_{1c} level of 6.9% reached or to standard blood glucose control with a hemoglobin A_{1c} level of 8.4% reached [13]. At 5.6-year median follow-up, the primary outcome of the time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease, and amputation for ischemic gangrene and the incidence of all-cause mortality were not significantly different between both treatment groups [13]. The incidence of microvascular complications was not significantly different between both treatment groups [13]. The incidence of adverse events, predominantly hypoglycemia, was 24.1% with a hemoglobin A_{1c} level of 6.9% reached versus 17.6% with a hemoglobin A_{1c} level of 8.4% reached [13].

In a retrospective observational study of 26,673 patients with Type 2 diabetes mellitus, mean age 59.1 years, enrolled in Kaiser Permanente Northwest, at a mean follow-up of 6 years, compared with those who had a hemoglobin A_{1c} level of 7.0% to 7.4%, those with a hemoglobin A_{1c} level of less than 6.0% had a significant 68% increased risk of cardiovascular disease hospitalization, those with a hemoglobin A_{1c} level of 6.0% to 6.4% had a significant 18% increased risk of cardiovascular disease hospitalization, those with a hemoglobin A_{1c} level of 6.5% to 6.9% had a significant 18% increased risk of cardiovascular disease hospitalization, those with a hemoglobin A_{1c} level of 8.5% to 8.9% had a significant 55% increased risk of cardiovascular disease hospitalization, and those with a hemoglobin A_{1c} level of 9.0% or higher had a significant 83% increased risk of cardiovascular disease hospitalization [14]. Compared with those who had a hemoglobin A_{1c} level of 7.0% to 7.4%, all-cause mortality was significantly increased from 12.2% to 20.4% in those with a hemoglobin A_{1c} level of less than 6.0%, from 12.2% to 16.2% in those with a hemoglobin A_{1c} level of 6.0% to 6.4%, from 12.2% to 13.4% in those with a hemoglobin A_{1c} level of 6.5% to 6.9%, and from 12.2% to 15.3% in those with a hemoglobin A_{1c} level of 9.0% or higher [14].

Severe hypoglycemia may be associated with cardiovascular events and death [15]. Severe hypoglycemia may cause ischemic cerebral changes with neurologic deficits [16, 17], atrial fibrillation [18], and ischemic electrocardiographic abnormalities [19].

A scientific statement from the American Heart Association and the American Diabetes Association in 2007 recommended that the hemoglobin A_{1c} level in patients with diabetes mellitus should be less than 7.0% and as close to less than 6.0% as possible without causing significant hypoglycemia [20]. The American Heart Association/American College of Cardiology Foundation 2011 secondary prevention guidelines in patients with coronary and other atherosclerotic vascular disease recommend a target hemoglobin A_{1c} level of less than 7.0% in patients with diabetes mellitus [21]. However, these guidelines recommend that less stringent hemoglobin A_{1c} levels may be considered for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbidities, or those in whom the goal is difficult to reach despite intensive therapy [21].

The American Diabetes Association 2013 guidelines state that a reasonable hemoglobin A_{1c} goal for many nonpregnant adults with diabetes mellitus is less than 7.0% [22]. A hemoglobin A_{1c} level of less than 6.5% may be considered in adults with a short duration of diabetes mellitus, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment [22]. A hemoglobin A_{1c} level of less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular or microvascular complications, extensive comorbidities, and long-standing diabetes mellitus in whom the hemoglobin A_{1c} goal is difficult to attain despite multiple glucose-lowering drugs including insulin [22].

The 2013 American Geriatrics Society guidelines for improving the care of older adults with diabetes mellitus recommend that the hemoglobin A_{1c} level generally should be between 7.5% to 8.0% [23]. A hemoglobin A_{1c} level between 7.0% and 7.5% may be appropriate if it can be safely achieved in the elderly with few comorbidities and a good functional status.

Hemoglobin A_{1c} levels between 8.0% and 9.0% are appropriate for elderly adults with multiple comorbidities, poor health, and limited life expectancy. These guidelines also state that there is potential harm in lowering the hemoglobin A_{1c} level to less than 6.5% in older adults [23]. For adults younger than 65 years of age, using drugs to lower the hemoglobin A_{1c} level to less than

6.5% is associated with harms, including hypoglycemia and mortality, except for reductions in myocardial infarction and death with metformin [6]. In frail older adults, patients with limited life expectancy or extensive comorbid conditions, and in patients in whom the risks of intensive glycemic control appear to outweigh the potential benefits, a less stringent hemoglobin A_{1c} level such as 8.0% is appropriate [22, 23].

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