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EDITORIAL

Editorial on hemoglobin A1c, blood pressure, and low-density lipoprotein cholesterol goals in diabetics

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Abstract

The American Diabetes Association (ADA) 2013 guidelines state that a reasonable hemoglobin A1c goal for many nonpregnant adults with diabetes is less than 7.0% a hemoglobin A1c level of less than 6.5% may be considered in adults with short duration of diabetes, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment. A hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, extensive comorbidities, and long-standing diabetes in whom the hemoglobin A1c goal is difficult to attain despite multiple glucose-lowering drugs including insulin. The ADA 2013 guidelines recommend that the systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg. These guidelines also recommend use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the treatment of hypertension in diabetics unless they are pregnant. Diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol lowered to less than 70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL. Combination therapy of a statin with either a fibrate or niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not recommended. Hypertriglyceridemia should be treated with dietary and lifestyle changes. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis.

Key words: Diabetes mellitus; Blood pressure; Hemoglobin A1c; Serum low-density lipoprotein cholesterol; Statins; Lipid-lowering drugs

Core tip: 2013 guidelines state that a reasonable hemoglobin A1c goal for diabetics is less than 7.0% a hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, and extensive comorbidities. The systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg. Diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol lowered to less than 70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL. Combination therapy of a statin with either a fibrate or niacin is not recommended.

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INTRODUCTION

The American Diabetes Association (ADA)/American Heart Association (AHA) 2007 scientific statement recommended that diabetics should have a hemoglobin A1c level less than 7.0% and as close to normal (less than 6.0%) without causing significant hypoglycemia[1]. This scientific statement also recommended that diabetics with hypertension should have their blood pressure lowered to less than 130/80 mmHg[1]. In addition, this scientific statement recommended that combination therapy of statins with fibrates or niacin may be necessary to achieve lipid targets. This editorial will discuss clinical trial data showing why these recommendations needed to be changed.

HEMOGLOBIN A1C GOALS

The action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation trial randomized 11140 type 2 diabetics, mean age 66 years, to intensive glucose control with a hemoglobin A1c of 6.5% reached or to standard glucose control with a hemoglobin A1c of 7.3% reached[2]. At 5-year median follow-up, death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke and all-cause mortality were similar in both treatment groups. Severe hypoglycemia occurred in 2.7% of the intensive glucose control group *vs* 1.5% in the standard glucose control group (hazard ratio = 1.86; 95%CI: 1.42-2.40; $P < 0.001$)[2]. However, major microvascular events (new or worsening nephropathy or retinopathy) were reduced from 10.9%-9.4% by intensive glucose control (hazard ratio = 0.86; 95%CI: 0.77-0.97; $P = 0.01$), primarily because of a reduction in nephropathy[2].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group randomized 10251 type 2 diabetics, mean age 62.2 years, to intensive glucose control with a hemoglobin A1c of 6.4% reached or to standard glucose control with a hemoglobin A1c of 7.5% reached[3]. At 3.5-year mean follow-up, the incidence of cardiovascular death, nonfatal MI, or nonfatal stroke was not significantly different between both treatment groups. However, all-cause mortality was 5.0% in the intensive glucose control group *vs* 4.0% in the standard glucose control group (hazard ratio = 1.22; 95%CI: 1.01-1.46; $P = 0.04$). Hypoglycemia requiring medical assistance occurred in 10.5% of the intensive glucose control group *vs* 3.5% in the standard glucose control group ($P < 0.001$)[3].

The Veterans Affairs Diabetes Trial randomized 1791 type 2 diabetics, mean age 60.4 years, to intensive glucose control with a hemoglobin A1c of 6.9% reached or to standard glucose control with a hemoglobin A1c of 8.4% reached[4]. At 5.6-year median follow-up, cardiovascular death, nonfatal MI, nonfatal stroke, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease, or amputation for ischemic gangrene and all-cause mortality were not significantly different between both treatment groups. Microvascular complications were not significantly different between both treatment groups. Adverse events, predominantly hypoglycemic episodes were more frequent in the intensive glucose treatment group (24.1% *vs* 17.6%, $P < 0.001$)[4].

The ADA 2013 guidelines state that a reasonable hemoglobin A1c goal for many nonpregnant adults with diabetes is less than 7.0%[5]. A hemoglobin A1c level of less than 6.5% may be considered in adults with short duration of diabetes, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment. A hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, extensive comorbidities, and long-standing diabetes in whom the hemoglobin A1c goal is difficult to attain despite multiple glucose-lowering drugs including insulin[5].

The American Geriatrics Society website on February 21, 2013 stated that reasonable glycemic targets would be hemoglobin A1c levels of 7.0%-7.5% in older adults with long life expectancy, 7.5%-8.0% in older adults with moderate comorbidities and a life expectancy of less than 10 years, and 8.0%-9.0% in older adults with multiple comorbidities and shorter life expectancy. Tight control of blood sugar causes higher rates of hypoglycemia in older adults.

BLOOD PRESSURE GOALS

The 2009 European Society of Hypertension guidelines recommended that lowering the blood pressure to less than 130/80 mmHg in patients at high risk for cardiovascular events was unsupported by prospective trial data, and that the systolic blood pressure should be lowered to less than 140 mmHg in these patients[6]. The American College of Cardiology Foundation/AHA 2011 expert consensus document on hypertension in the elderly recommended that the blood pressure should be reduced to less than 140/90 mmHg in adults younger than 80 years at high risk for cardiovascular events[7]. On the basis of data from the Hypertension in the Very Elderly trial[8], these guidelines recommended that the systolic blood pressure should be reduced to 140-145 mmHg if tolerated in adults aged 80 years and older[7].

In the International Verapamil SR-Trandolapril Study, 6400 patients had diabetes mellitus and coronary artery disease[9]. These patients were categorized as having tight control of their blood pressure if they could maintain their systolic blood pressure below 130 mmHg and their diastolic blood pressure below 85 mmHg, usual control if they could maintain their systolic blood pressure between 130-139 mmHg, and uncontrolled if their systolic blood pressure was 140 mmHg or higher. During 16893

patient-years of follow-up, a cardiovascular event rate (all-cause mortality, nonfatal MI, or nonfatal stroke) of 12.6% occurred in patients with usual control of blood pressure *vs* 19.8% in patients with uncontrolled hypertension (adjusted hazard ratio = 1.46; 95%CI: 1.25-1.71; $P < 0.001$) [9]. The incidence of cardiovascular events was 12.6% in patients with usual control of blood pressure *vs* 12.7% in patients with tight control of blood pressure (*P* not significant). The all-cause mortality rate was 11.0% with tight control of blood pressure *vs* 10.2% with usual control of blood pressure ($P = 0.06$). When extended follow-up to 5 years following the close of INVEST was included, the all-cause mortality rate was 22.8% with tight control of blood pressure *vs* 21.8% with usual control of blood pressure (adjusted hazard ratio = 1.15; 95%CI: 1.01-1.32; $P = 0.04$)[9].

The ACCORD blood pressure trial randomized 4733 patients with type 2 diabetes mellitus to intensive blood pressure control with a target systolic blood pressure of less than 120 mmHg or to standard blood pressure control with a target systolic blood pressure less than 140 mmHg[10]. After 1 year, the mean systolic blood pressure was 119.3 mmHg in the intensive blood pressure control group *vs* 133.5 mmHg in the standard blood pressure control group. Mean follow-up was 4.7 years. The primary composite outcome of nonfatal MI or nonfatal stroke or cardiovascular death and the annual rate of death from any cause were not significantly different between both treatment groups. The annual stroke rate was 0.32% in the intensive blood pressure control group *vs* 0.53% in the standard blood pressure control group (hazard ratio = 0.59; 95%CI: 0.39-0.89; $P = 0.01$) (number needed to treat to reduce 1 stroke = 476 patients). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive blood pressure control group *vs* 1.27% of the standard blood pressure control group, $P < 0.001$ (number needed to treat to increase 1 serious adverse event = 49 patients)[10].

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint trial included 9603 diabetics, mean age 66.1 years, and 15981 nondiabetics, mean age 66.6 years, with hypertension at high risk for cardiovascular events[11]. Mean follow-up was 4.6 years. The primary endpoint was cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure. Compared to nondiabetics, diabetics had a 48% significant increase in the primary endpoint (hazard ratio = 1.48; 95%CI: 1.38-1.57). In patients with and without diabetes, antihypertensive drug treatment reduced the primary outcome if the baseline systolic blood pressure was 143 to 155 mmHg. The lowest incidence of death from cardiovascular causes in diabetics occurred with a systolic blood pressure of 135.6 mmHg (range 130.6 to 140.5 mmHg). The lowest incidence of death from cardiovascular causes in nondiabetics occurred with a systolic blood pressure of 133.1 mmHg (range 128.8 to 137.4 mmHg). For the primary outcome, the highest risk in those with and without diabetes occurred in patients with the lowest or highest in-trial diastolic blood pressures (67.2 and 86.7 mmHg, respectively)[11].

The ADA 2013 guidelines recommend that the systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg[5]. These guidelines also recommend use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the treatment of hypertension in diabetics unless they are pregnant[5].

DYSLIPIDEMIA

Numerous studies have demonstrated that statins reduce cardiovascular events including stroke and mortality in diabetics[12-15]. A meta-analysis was performed of 14 randomized trials of statins used to treat 18686 diabetics (1466 with type 1 diabetes and 17220 with type 2 diabetes)[14]. Mean follow-up was 4.3 years. All-cause mortality was reduced 9% per mmol/L reduction in serum low-density lipoprotein (LDL) cholesterol, $P = 0.02$. Major cardiovascular events were reduced 21% per mmol/L reduction in serum LDL cholesterol, $P < 0.0001$. Statins caused in diabetics a 22% reduction in MI or coronary death ($P < 0.0001$), a 25% reduction in coronary revascularization ($P < 0.0001$), and a 21% reduction in stroke ($P = 0.0002$). After 5 years, 42 fewer diabetics per 1000 diabetics treated with statins had major cardiovascular events[15].

In the Fenofibrate Intervention and Event Lowering in Diabetes study, 9795 type 2 diabetics (2131 with cardiovascular disease) were randomized to fenofibrate or placebo[16]. Mean follow-up was 5.0 years. The primary outcome of coronary events was not significantly reduced by fenofibrate. Fenofibrate insignificantly increased CAD mortality 19%[16].

In the ACCORD trial, 5518 type 2 diabetics at high risk for cardiovascular disease were randomized to simvastatin plus fenofibrate or to simvastatin plus placebo[17]. Mean follow-up was 4.7 years. Compared with simvastatin plus placebo, simvastatin plus fenofibrate did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke. Among 3414 patients with atherosclerotic cardiovascular disease and low serum high-density lipoprotein (HDL) cholesterol levels treated with simvastatin plus ezetimibe if needed to maintain the serum LDL cholesterol less than 70 mg/dL, at 36-mo follow-up, patients randomized to niacin had improvements in serum HDL cholesterol and triglyceride levels but no clinical improvement compared to patients randomized to placebo[18].

Professor Jane Armitage presented on March 9, 2013 at the Annual Scientific Meeting of the American College of Cardiology in San Francisco, California the results of HPS_2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events). In this study of 25673 patients at high risk of cardiovascular events, adding extended-release niacin plus the anti-flushing agent laropriprant to treatment

with simvastatin or simvastatin/ezetimibe did not reduce at 3.9-year follow-up cardiovascular events. However, there were 31 serious adverse events among every 1000 niacin-treated patients including 3.7% excess diabetic complications ($P < 0.0001$) and 1.8% excess new onset diabetes ($P < 0.0001$).

Diabetics at high risk for cardiovascular events should have their serum LDL cholesterol lowered to less than 70 mg/dL with statins[5]. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL[5]. Combination therapy of a statin with either a fibrate or niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not recommended[5]. Hypertriglyceridemia should be treated with dietary and lifestyle changes[5]. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis[5].

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