Hemoglobin A1c, Blood Pressure, and Serum Low-Density Lipoprotein Cholesterol Goals in Diabetics

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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 reduced to less than 130/80 mm Hg [1]. In addition, this scientific statement recommended that combination therapy of statins with fibrates or niacin may be necessary to achieve lipid targets. [1]. This editorial will discuss clinical trial data showing that these recommendations needed to be changed.

Hemoglobin A1c Goals

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial randomized 11, 140 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, cardiovascular death or 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 versus 1.5% in the standard glucose control group (hazard ratio=1.86, p<0.001) [2].

The Action to control Cardiovascular Risk in Diabetes (ACCORD) Study Group randomized 10,251 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% in the intensive glucose control group versus 4% in the standard glucose control group (hazard ratio=1.22, p=0.04) [3]. Hypoglycemia requiring medical assistance occurred in 10.5% of the intensive glucose control group versus 3.5% in the standard glucose control group (p<0.001) [3].

The Veterans Affairs Diabetes Trial (VADT) randomized 1, 791 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, or nonfatal stroke and all-cause mortality were not significantly different between both treatment groups. Hypoglycemic episodes were more frequent in the intensive glucose treatment group (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 [5]. 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% to 7.5% in older adults with long life expectancy, 7.5% to 8.0% in older adults with moderate comorbidities and a life expectancy of less than 10 years, and 8.0% to 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 mm Hg 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 mm Hg 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 lowered to less than 140/90 mm Hg 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 to 145 mm Hg if tolerated in adults aged 80 years and older [7].

In the International Verapamil SR-Trandolapril Study, 6,400 patients had diabetes mellitus and coronary artery disease (CAD) [9]. These patients were categorized as having tight control of their blood pressure if they could maintain their systolic blood pressure below 130 mm Hg and their diastolic blood pressure below 85 mm Hg, usual control if they could maintain their systolic blood pressure between 130 to 139 mm Hg, and uncontrolled if their systolic blood pressure was 140 mm Hg or higher. During 16,893 patient-years of follow-up, a cardiovascular event rate of 12.6% occurred in patients with usual control of blood pressure versus 19.8% in patients with uncontrolled hypertension (adjusted hazard ratio=1.46, p<0.001) [9]. The incidence of cardiovascular events was 12.6% in patients with usual control of blood pressure versus 12.7% in patients with tight control of blood pressure (p not significant). The all-cause mortality rate was 11% with

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tight control of blood pressure versus 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 versus 21.8% with usual control of blood pressure (adjusted hazard ratio=1.15, p=0.04) [9].

The ACCORD blood pressure trial randomized 4,733 patients with type 2 diabetes mellitus to intensive blood pressure control with a target systolic blood pressure of less than 120 mm Hg or to standard blood pressure control with a target systolic blood pressure less than 140 mm Hg [10]. After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive blood pressure control group versus 133.5 mm Hg 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 [10] The annual stroke rate was 0.32% in the intensive blood pressure control group versus 0.53% in the standard blood pressure control group, 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 versus 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 ADA 2013 guidelines recommend that the systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mm Hg [5]. These guidelines also recommend use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the treatment of hypertension in diabetics [5].

Dyslipidemia

Numerous studies have demonstrated that statins reduce cardiovascular events including stroke and mortality in diabetics [11-14]. A meta-analysis was performed of 14 randomized trials of statins used to treat 18, 686 diabetics (1,466 with type 1 diabetes and 17,220 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 1,000 diabetics treated with statins had major cardiovascular events [14].

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9,795 type 2 diabetics (2,131 with cardiovascular disease) were randomized to fenofibrate or placebo [15]. 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% [15].

In the ACCORD trial, 5,518 type 2 diabetics at high risk for cardiovascular disease were randomized to simvastatin plus fenofibrate or to simvastatin plus placebo [16]. 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 [16]. Among 3,414 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-month 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 [17].

Diabetics at high risk for cardiovascular events should have their serum LDL cholesterol reduced 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].

References

1. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, et al. (2007) Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 30: 162-172.

2. Patel A, MacMahon S, Chalmers J, Neal B, et al. (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358: 2560-2572.

3. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, et al. (2008) Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358: 2545-2559.

4. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, et al. (2009) Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 360: 129-139.

5. American Diabetes Association (2013) Standards of medical care in diabetes--2013. Diabetes Care 1: S11-66.

6. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, et al. (2009) Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. Blood Press 18: 308-347.

7. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, et al. (2011) ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Coll Cardiol 57: 2037-2114.

8. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, et al. (2008) Treatment of hypertension in patients 80 years of age or older. N Engl J Med 358: 1887-1898.

9. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, et al. (2010) Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 304: 61-68.

10. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, et al. (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362: 1575-1585.

11. Aronow WS, Ahn C, Gutstein H (2002) Reduction of new coronary events and new atherothrombotic brain infarction in older persons with diabetes mellitus, prior myocardial infarction, and serum low-density lipoprotein cholesterol >/=125 mg/dl treated with statins. J Gerontol A Biol Sci Med Sci 57: M747-M750.

12. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group (2003) MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 361: 2005-2016.

13. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, et al. (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes mellitus in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. Lancet 364: 685-696.

14. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell

L, Collins R, Keech A, et al. (2008) Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 371: 117-125.

15. Keech A, Simes RJ, Barter P, Best J, Scott R, et al. (2005) Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 366: 1849-1861.

16. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, et al. (2010) Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 362: 1563-1574.

17. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, et al. (2011) Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 365: 2255-2267.