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Review

Evolving Targets for Risk Reduction in Diabetes

GREGORY M. CAPUTO, M.D., FACP, JOEL B. BRAUNSTEIN, M.D.,* ROGER S. BLUMENTHAL, M.D., FACC*

Department of Medicine, Penn State College of Medicine, Hershey, Pennsylvania; *Division of Cardiology, The Johns Hopkins Medical Institutions. Baltimore, Maryland, USA

Summary: Recent evidence shows that target low-density lipoprotein cholesterol should be less than 100 mg/dl in patients with diabetes, and that even those with initially low levels benefit from pharmacologic therapy. Recent studies document that blood pressures lower than the previous target of 140/90 mmHg are beneficial, in addition to providing observational evidence against a lower threshold of benefit. Evidence that addresses the effect of blood glucose on macrovascular disease risk in patients with diabetes is reviewed. Finally, recommendations are made regarding systematic changes in healthcare delivery that will facilitate risk reduction strategies in diabetes.

Key words: diabetes mellitus, blood pressure, hypertension, hyperlipidemia, glucose, lipids, cholesterol

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes. In 1998, a pivotal study demonstrated that diabetic patients without known coronary artery disease (CAD) have similar 7-year CAD outcomes as do nondiabetic patients with prior myocardial infarction,[1] establishing diabetes as a coronary disease equivalent.

Current target levels for low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), blood pressure (BP), and blood glucose for individuals with diabetes are as low and aggressive as ever. Rapidly emerging evidence from well-designed trials, however, challenge these target levels. We evaluate current treatment goals for individuals with diabetes and assess whether these guidelines are likely to be sufficient for optimizing patients' long-term health outcomes.

Address for reprints:

Gregory M. Caputo, M.D., FACP
Division of General Internal Medicine
500 University Drive
Hershey, PA 17033, USA
e-mail: gcaputo@psu.edu

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Lipid Management

The benefits of statin therapy in patients with diabetes are well documented;[2–4a] however, well-defined targets for the optimal level of LDL-C generally lack prospective validation. The recent National Cholesterol Education Program Adult Treatment Panel (ATP-III) guidelines recommend a target level of < 100 mg/dl for all patients with diabetes mellitus.[5] The results of the largest prospective trial to evaluate the marginal gain in treatment efficacy achieved with lower targets of LDL-C reduction were recently published.[4] The Heart Protection Study (HPS) enrolled approximately 20,000 patients at high risk for vascular events, 5,963 of whom had diabetes. After approximately 5 years, patients with diabetes treated with simvastatin 40 mg achieved a 19% relative risk reduction for the development of vascular events. The absolute risk reduction was 4.9%, indicating a number needed to treat of only 20 diabetic patients to prevent one major vascular event. There was no initial LDL-C threshold for which simvastatin provided benefit—even subjects with initial LDL-C levels < 100 mg/dl achieved an approximately 25% relative risk reduction with simvastatin treatment.

Blood Pressure Management

Approximately 40% of individuals with diabetes have hypertension at the time of diagnosis,[6] which markedly increases the risk of CAD, peripheral arterial disease, stroke, nephropathy, and retinopathy.[7] The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommended a target BP < 130/85 mmHg for patients with both diabetes and hypertension.[8] Since 1997, studies have suggested additional benefit from further blood pressure reductions. In the subset of 1,500 diabetic subjects in the Hypertension Optimal Treatment (HOT) study,[9] a target diastolic blood pressure (DBP) level of ≤ 80 mmHg resulted in an approximate 50% relative risk reduction in cardiovascular events,

compared with those whose target DBP was ≤ 90 mmHg. Benefits occurred without a lower threshold for DBP. In the United Kingdom Prospective Diabetes Study (UKPDS), every 10% reduction in mean BP led to an 11 and 15% reduction in myocardial infarction and death rates, respectively. Patients with systolic blood pressure (SBP) < 120 mmHg had the lowest risk, and no lower threshold of risk existed.[6, 10] Thus, based on evidence from UKPDS and the HOT study, a target of 120/80 mmHg may be an even more reasonable target BP than the recently recommended target of 130/80 mm Hg as proposed by the National Kidney Foundation.[11]

The cardiovascular benefits of the angiotensin-converting enzyme (ACE) inhibitor ramipril for individuals with diabetes were documented in the Heart Outcomes Prevention Evaluation (HOPE) trial.[12] Among the 3,577 subjects with diabetes, those treated with ramipril (compared with placebo) for 4.5 years had a lower risk of death by 24%, myocardial infarction by 22%, and stroke by 33%. In the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE),[13] a HOPE substudy, ramipril led to dose-dependent decreases in carotid artery atherosclerosis progression as measured by B-mode ultrasonography. The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) demonstrated superior effectiveness of the angiotensin receptor blocker (ARB) losartan over the beta blocker atenolol with regard to cardiovascular outcomes[14] in the subgroup of patients with diabetes, hypertension, and left ventricular hypertrophy. The Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) studies showed that ARBs significantly slow renal decline and reduce the development of end-stage renal disease in diabetics with significant proteinuria and mild to moderate baseline renal dysfunction.[15–17]

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) challenged the superiority of ACE inhibitors over other classes in preventing vascular events.[18] Even in the 36% of subjects with diabetes, the thiazide diuretic chlorthaladone was superior to the ACE inhibitor lisinopril for several cardiovascular endpoints, but this study did not evaluate target BP.

Blood Glucose Management

Poor glycemic control is a risk factor for CAD,[19–22] but as yet there is no conclusive evidence that treatment regimens resulting in tighter glycemic control reduce CAD risk. However, in the UKPDS, among patients randomized to receive metformin, all-cause deaths were reduced by 46% compared with conventionally treated patients. Metformin use was also associated with a 30% relative risk reduction in myocardial infarction compared with conventional treatment regimens.[23] Of note, a recent study documented that progression of carotid artery intima-media thickness was significantly less in the intensive treatment group compared with the standard treatment group of the Diabetes Control and Complications Trial.[23a]

Of course, microvascular complications are reduced with intensive glucose control, and there is no apparent lower threshold of benefit. The American College of Endocrinologists has formally acknowledged this principle by recommending hemoglobin A1C levels < 6.5% as a treatment target in their most recent set of guidelines on glycemic management among individuals with diabetes.[24]

The metabolic syndrome consists of insulin resistance, hypertension, dyslipidemia, and obesity. The presence of metabolic syndrome increases the risk of CAD in patients with type 2 diabetes.[25] Thiazolidinediones hold promise as a pharmacologic class of compounds that may reduce cardiac risk in patients with the metabolic syndrome. Thiazolidinediones such as pioglitazone and rosiglitazone are already widely used for treating hyperglycemia in individuals with diabetes. These agents are peripheral insulin sensitizers and appear to have positive effects on lipoprotein metabolism. While a superior agent is unclear, one randomized trial comparing the effects of rosiglitazone and pioglitazone on lipid levels has demonstrated that improvements were confined to only individuals treated with pioglitazone.[26] Thiazolidinediones hold promise for other reasons as well, including their ability to impart favorable changes in the vascular endothelium, reduce cytokine production by proatherogenic macrophages, and possibly lower blood thrombogenicity.[27, 28]

Metformin also remains a commonly used agent to treat patients with type 2 diabetes. It reduces insulin resistance, inhibits prothrombotic factor activity, and enhances lipoprotein metabolism in diabetic and insulin-resistant nondiabetic patients.[29, 30] In addition, both metformin and the thiazolidinedione ciglitazone reduce interleukin-8 production, a cytokine that has possible implications in atherogenesis.[31] At present, the primary clinical utility of metformin and thiazolidinediones is in improving glycemic control in patients with diabetes. However, these agents may have a broader future for nondiabetic patients with metabolic syndrome or for those at high risk of metabolic syndrome development.

Clearly, the critical importance of diagnosing the metabolic syndrome relates to its impact on cardiovascular risk so as to intensify risk reduction management.

Conclusions

We strongly urge cardiologists to reduce risk factors aggressively in patients with diabetes. The exact targets, however, are rapidly evolving. Current recommendations are based on the best available evidence at the time of their publication. The ATP-III guidelines identify an LDL-C of < 100 mg/dl as the primary lipid goal for all patients with diabetes, yet new trial evidence suggests that substantial benefits are gained even if the initial LDL-C is < 100 mg/dl.[4a] The Heart Protection Study provides a compelling argument to lower the current LDL-C threshold for initiating lipid-lowering therapy in high-risk individuals, including those with diabetes. Evidence for BP reductions to < 120/80 mmHg, as supported by the HOT and UKPDS studies challenge current standards outlined by JNC

VI and the National Kidney Foundation. With regard to glycemic maintenance, new guidelines support target hemoglobin A1C levels < 6.5% for optimal long-term microvascular risk reduction.[24]

There is concern that the U.S. healthcare system is ill equipped to meet the demands of full implementation of current guidelines at the present time, given the evidence that cardiovascular disease risk reduction strategies are inconsistently and poorly implemented in U.S. patients with diabetes.[32] The basis for concern is also well exemplified by a number of recently published reports documenting process inadequacies,[33–35] wherein scientific knowledge failed to translate into clinical practice. Data from the Third National Health and Nutrition Examination Survey demonstrate that approximately 60% of patients with type 2 diabetes fail to achieve HbA1C levels ≤ 7 mg/dl and 60% are inadequately treated for hypertension and hyperlipidemia.[36]

In a review by Phillips *et al.*,[37] provider and system shortcomings may largely explain why patients frequently fail to achieve desired BP , cholesterol, and glycemic goals. The authors use the phrase "clinical inertia" to denote the "failure of health care providers to initiate or intensify therapy when indicated." The authors proposed that clinical inertia could be explained by three factors: physician self-overestimation of care provided to patients, use of "soft" indications to avoid therapy intensification, and lack of physician education and training as well as practice organization directed at achieving therapeutic goals.[37]

Fortunately, clinical inertia is not immune to change. Physician behavior is modifiable and may be particularly responsive to creative new designs in quality improvement.[38] Quality of care initiatives should aim at identifying inefficiencies in the system and implement necessary tools of change. New approaches to medical education and quality-based incentives for practicing clinicians may stimulate provider behavioral changes that should improve the effectiveness of patient care.

The evidence-based model of diabetes healthcare delivery supports a change from the provision of reactive, acute care (e.g., treating long-term complications) to the provision of preventive, chronic care (e.g., aggressive risk factor reduction). Achieving optimal levels of risk factor control in the current population of diabetic patients is a critical first goal. The second goal is for the development of new system-based initiatives that establish ways to identify high-risk prediabetic and diabetic individuals who are unaware of this diagnosis. The third goal should be a rapid incorporation of newly published, effective preventive interventions into treatment guidelines and routine clinical practice. Only then will we be able to claim that we are sufficiently addressing the high burden of cardiovascular disease among our patients with diabetes mellitus.

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