

The following abstracts, from peer-reviewed journals containing literature on type 2 diabetes and its management, were selected for their relevance to this Special Report supplement.

Insulin Resistance Increases Cardiovascular Risks in Individuals with Type 2 Diabetes

The inability of cells and tissues to use insulin efficiently (ie, insulin resistance) has long been associated with cardiovascular risk factors in nondiabetic individuals. This study evaluated the relationship between insulin sensitivity determined by frequently sampled intravenous glucose tolerance tests and by lipid levels, blood pressure, coagulation factors, and a carotid ultrasonic index of atherosclerosis in a geographically diverse population of 479 subjects with type 2 diabetes. None of the subjects was taking metformin or other insulin-sensitizing agents. Only 8% (37/479) of the subjects were insulin sensitive (defined as having a test value above the median observed in the nondiabetic counterpart of that same population). Insulin resistance was significantly correlated with atherogenic changes in several cardiovascular factors, including elevations in the levels of total triglyceride, very low density lipoprotein (VLDL) cholesterol, VLDL triglyceride, fibrinogen, plasminogen activation inhibitor 1, and fasting glucose. Insulin resistance was inversely correlated with the high-density lipoprotein (HDL) cholesterol level and with low-density lipoprotein (LDL) particle size. The carotid intimal medial thickness was

greater in those with insulin resistance, as was shown previously in subjects without diabetes, but the difference was not statistically significant. Most correlations remained significant even after adjustment for demographic characteristics, obesity, and body weight distribution. The study shows that insulin sensitivity is related to cardiovascular risk in individuals with type 2 diabetes.

Paffner SM, D'Agostino R, Mykkanen L, et al. Insulin sensitivity in subjects with type 2 diabetes. *Diabetes Care* 1999;22:562-568.

Glycemic Control Enables Diabetic Patients to Feel Better and Incur Less Treatment Cost

Classic studies of treatment for type 2 diabetes have documented reductions in long-term microvascular complications. In this double-blind, randomized, placebo-controlled trial, the effects of good glycemic control on short-term quality-of-life and economic outcomes were measured. Patients already being treated with sulfonyl-ureas or diet underwent a 3-week washout period and were randomized to 12 weeks of placebo or glipizide gastrointestinal therapeutic system (GITS). The mean hemoglobin A1c (HbA1c) level was significantly lowered in those on active treatment (7.5%) versus those who received placebo (9.3%). Subjects who received active treatment exhibited significant improvements in several quality-of-life characteristics, including symptom distress, general perceived distress, general perceived health, cognitive functioning, and overall visual analogue scale

(VAS) ratings. Those who received placebo reported more hyperglycemia-type symptoms. Treatment differences were especially apparent in terms of VAS emotional health, general health, sleep, depression, disorientation and detachment, and vitality. Differences between the 2 groups with respect to the symptoms of hypoglycemia were not significant. Those treated with the sulfonylurea also had more favorable economic outcomes, including higher retained employment (97% vs 85%), greater productive capacity (99% vs 87%), less absenteeism (\$24 vs \$115 loss per worker per month), fewer bed days (\$1539 vs \$1843 per 1000 person-days), and fewer restricted-activity days (\$2660 vs \$4275 per 1000 person-days). As quality of life improved as a result of better glycemic control, overall healthcare use decreased. This study is 1 of the first to document the short-term clinical and economic benefits of glycemic control in patients with type 2 diabetes.

Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus. *JAMA* 1998;280:1490-1496.

Estimating the Extra Costs of Managing the Complications of Diabetes

The incidences of 6 diabetic complications over a 3-year period in a managed care population were determined from a retrospective review of patient records. The average age of the population was 61 years. More than 83% of the health maintenance organization (HMO) members were receiving

either no drugs or oral hypoglycemic agents, which suggests that most of those individuals had type 2 diabetes. Complication rates in 8905 patients with type 1 or 2 diabetes were consistently higher than those observed in 36,520 members (matched controls) without diabetes: myocardial infarction, 9.0% versus 3.2%; stroke, 8.7% versus 3.8%; hypertension, 26.2% versus 16.9%; end-stage renal disease, 5.9% versus 1.4%; foot ulcer, 7.9% versus 1.1%; and eye disease, 44.3% versus 2.8%. Total per-member costs of care were determined with an HMO automated accounting system. Overall, the annual costs of care for those with diabetes were \$8716 versus \$3999 for the matched controls. Because medical costs and accounting systems vary so much from health system to health system, the authors reported the excess treatment costs for complications in relative rather than absolute terms. Thus, expressed as a multiple of the average cost of care for nondiabetic members (older than 65 years of age) without a particular complication, the excess expenditures to treat diabetic patients with the complications in the year after diagnosis were as follows: no complications, 1.59 times; myocardial infarction, 4.1 times; stroke, 3.5 times; hypertension, 2.6 times; end-stage renal disease, 4.3 times; foot ulcer, 4.0 times; and eye disease, 2.5 times. In younger patients, the multiples were even higher (eg, myocardial infarction, 8.6 times; stroke, 7.5 times; foot ulcer, 8.6 times). The costs of care generally decreased in the second year after diagnosis for both cohorts of patients. The per-patient estimates of the costs of treating the complications of diabetes will be used by the HMO to predict the cost effectiveness of treatment and prevention strategies.

Ramsey SD, Newton K, Blough D, et al. Patient-level estimates of the cost of complications in diabetes in a managed-care population. *Pharmacoeconomics* 1999; 16:285-295.

Carveout Disease Management for Patients With Diabetes: How Much Better?

A private diabetes disease management company performed a retrospective review of short-term clinical and economic outcomes in approximately 7000 people with diabetes. Those individuals, who were members at 1 of 7 managed care plans contracting with the third-party vendor, were enrolled in a comprehensive diabetes management program that included features such as patient and provider profiling tools, automated reminders for screenings and tests, and case coordinators for complex cases. Data for the baseline months preceding enrollment in the program were compared with outcomes and costs after enrollment. In the "managed period," members were much more likely to undergo preventive tests on the schedules recommended by groups such as the American Diabetes Association and the National Committee for Quality Assurance. Annual testing rates increased from 34% to 76% for hemoglobin A1c (HbA1c) tests, from 23% to 40% for eye examinations, from 2% to 25% for foot examinations, and from 39% to 63% for cholesterol screenings. In those 1603 patients who had undergone at least 2 glucose tests, the HbA1c level decreased from 8.9% to 8.5%. Hospital admissions per 1000 diabetic members decreased from 239 in the baseline period to 196 in the managed

period (-18%), and the number of bed days decreased from 1336 to 1047 (-21%). In the 5 of 7 plans in which economic data were available, total costs decreased by \$44 per diabetic member per month (-10.9%). The cost reduction was greatest for inpatient (-26%) and outpatient (-10.4%) costs. Costs for nondiabetic patients during that time period did not decrease (eg, total costs increased by 1.4% and outpatient charges decreased by only 2.2%). Pharmacy costs increased by 14.6% over the study period, but the increase was even greater (16.4%) in nondiabetic patients. The authors concluded that the diabetes disease management program would translate into \$528,000 in gross savings in the first year per 1000 diabetic members.

Rubin RJ, Dietrich KA, Hawk AD. Clinical and economic impact of implementing a comprehensive diabetes management program in managed care. *J Clin Endocrinol Metab* 1998;83: 2635-2642.

Computer-Supported Care for Diabetic Patients in a Health Maintenance Organization: How Much Better?

In 1995, a large health maintenance organization (HMO) in southern California created a computer database used to guide and track the care given to the highest-risk subpopulation (30%) of its 8200 members with diabetes. Outcomes for those patients from 1995 to 1998 were compared with those from the other 70% of diabetic patients who received usual care from primary care

physicians. Some patients transferred from the computer-managed group to the "usual care" group during the study. Annual compliance with 3 screening tests was significantly higher in the computer-managed group: glycosylated hemoglobin (Ghb) testing, 84% versus 51%; serum lipid testing, 75% versus 49%; and urinary protein testing, 51% versus 7%. Follow-up testing of initially elevated Ghb results was also significantly higher in the managed group (77% vs 44%), although both groups exhibited an overall Ghb decrease from the first test to the second test. In HMO patients with initially elevated blood pressure, those in the computer-managed group demonstrated a significantly greater decline in blood pressure during the follow-up period (systolic, 139 mm Hg vs 146 mm Hg; diastolic, 76 mm Hg vs 82 mm Hg). Inpatient utilization in the computer-managed group decreased from 1.28 days/patient in 1995 to 0.63 days/patient in 1997, a significantly greater decline than that seen in the other group, which exhibited a decrease from 1.35 days/patient to 1.26 days/patient. The authors stated that the favorable utilization and screening results may be biased by a self-selection for motivated compliant patients in the computer-managed group. They concluded that a local computerized tracking system can leverage the efforts of providers to improve diabetes care and outcomes.

Domurat ES. Diabetes managed care and clinical outcomes: The Harbor City, California Kaiser Permanente Diabetes Care System. *Am J Manag Care* 1999;5:1299-1307.

■ Prioritizing Diabetes Interventions by Cost Effectiveness: A Review of the Literature

In this review of the literature pertaining to the treatment of diabetes, 17 widely practiced interventions were ranked according to their cost effectiveness. Two interventions (eye care and preconception care) were deemed "clearly cost saving" (defined as having 1 well-controlled study comparing intervention and nonintervention patients or a modeling analysis demonstrating benefits with eventual savings that exceeded the cost of intervention). Two interventions (nephropathy prevention in patients with type 1 diabetes and improved glycemic control) were "clearly cost effective" (a study or model demonstrating benefits that cost no more than did equivalent benefits produced by generally accepted interventions for other diseases (ie, less than \$25,000 spent per year of life or quality-adjusted life-year gained). Nephropathy prevention in type 2 diabetics and self-management training were classified as "possibly cost effective." According to the current literature, the costs of attaining a life-enhancing effect from all other interventions (eg, case management, medical nutrition therapy, self-monitoring of blood glucose, foot care, blood pressure control, lipid control, smoking cessation, exercise, or hemoglobin A1c monitoring) were unclear. The authors called for implementation, at the very least, of cost-saving and cost-effective interventions for diabetic patients.

Klonoff DC, Schwartz DM. An economic analysis of intervention for diabetes. *Diabetes Care* 2000;23:390-404.

Hemoglobin A1c: A Clear Marker of Future Health Status and Medical Costs

Despite evidence indicating the clinical benefits of good glycemic control, most diabetic patients do not attain a hemoglobin A1c (HbA1c) level below that recommended by the American Diabetes Association. To measure the impact of poor glycemic control on health system costs, the HbA1c levels (1992) and medical costs (1993–1995) for more than 3000 diabetic members of a health maintenance organization (HMO) were analyzed. Costs included diagnostic, pharmaceutical, laboratory, utilization, and inpatient and outpatient charges available on the HMO information system. For every 1% increase in the HbA1c level, the average 3-year medical care charges increased significantly, from \$8576 at 6% to \$8954 at 7% to \$9555 at 8% to \$10,424 at 9% to \$11,629 at 10%. In individuals with diabetes and hypertension or heart disease, the glycemia-related increases in cost were similar. In all groups, the cost increments were greatest at the highest glucose levels. For example, a 1% improvement in the HbA1c level from 10% to 9% in diabetic patients with heart disease and hypertension was associated with a 3-year cost difference of \$4116; the differential from 7% to 6% was \$1504. The researchers concluded that investments designed to reduce the HbA1c level in patients with diabetes are appropriate for economic as well as clinical reasons.

Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycemic control. *Diabetes Care* 1997;20:1847–1853.

Per-Patient Spending on Diabetes: An Analysis in a Health Maintenance Organization

The excess cost of managing diabetic members in a health maintenance organization (HMO) was calculated. An automated database was used to compare 1-year (1994) costs of medical care for 85,209 diabetic members with the costs for 85,209 age-matched and sex-matched nondiabetic members of an HMO. Cost areas related to the treatment of the most typical complications of diabetes were the focus of the analysis. Overall, the excess cost of care for a diabetic member each year was \$3494. Thus the cost of care for diabetic members was about 2.4 times that for nondiabetic members. The largest segment of excess costs (39%) was allocated to hospitalization; other sites of excess spending were outside referrals (28%), pharmacy (9.4%), and primary care (6.8%). A large proportion of the excess costs (59.1%) could not be categorized by the type of diabetes complication, but coronary heart disease was the largest of the identifiable complications of diabetes; it accounted for 17% of the total excess costs. Overall, the treatment of 6 long-term complications of diabetes (heart disease, renal disease, amputation, stroke, other vascular disease, or eye disease) accounted for approximately 38% of costs, versus just 3.3% for the treatment of acute complications. The authors concluded that a diabetes disease management program could reduce long-term complications and could also save money in managed care settings.

Selby JV, Ray GT, Zhang D, Colby CJ. Excess costs of medical care for

patients with diabetes in a managed care population. *Diabetes Care* 1997; 20: 1396-1402.

Angiotensin-Converting Enzyme Inhibitor Reduces Cardiovascular Risk in Patients With Diabetes

As a result of its purported protective effects on the vascular endothelium and kidney, the angiotensin-converting enzyme (ACE) inhibitor ramipril (10 mg/day) was tested in a placebo-controlled trial in diabetic patients (> 55 years of age) who had experienced either a prior cardiovascular event or who had at least 1 other cardiovascular risk factor. High blood pressure was not required for enrollment. The study also tested the effect of vitamin E on cardiovascular risk factors. A total of 3577 patients were enrolled and were monitored for 4.5 years, at which time

the study was terminated early because of the consistent ramipril benefits: reduced risks of myocardial infarction (-22%), stroke (-33%), and cardiovascular death (-37%). Overall, the reduction in the primary outcome (a combination of the 3 events just described) was 25% (P = 0.0004). The total mortality rate was reduced by 24% in the ramipril group, and overt nephropathy rates decreased by 24% (P = 0.027). Even after adjustment for changes in systolic and diastolic blood pressures, ramipril still lowered the primary outcome by 25% (P = 0.0004). The authors concluded that ramipril has a vasculoprotective and renoprotective effect in those with diabetes.

Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355: 253-259.