Tips from Other Journals

Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

No Added Benefit of Fenofibrate for Cardiovascular Risk in Diabetes Mellitus

Background: Statins reduce the increased cardiovascular risk seen in patients with type 2 diabetes mellitus, but do not eliminate it. Studies have shown conflicting results as to whether fibrates may also help reduce cardiovascular disease in this population. Ginsberg and colleagues used the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial to determine if combination lipid therapy could reduce cardiovascular risk in patients with type 2 diabetes.

The Study: A total of 5,518 patients with type 2 diabetes were randomized to receive simvastatin (Zocor) at 40 mg per day or less, in addition to fenofibrate (Tricor; initial dosage of 160 mg per day) or placebo. All patients had an A1C level of 7.5 percent or more, a low-density lipoprotein cholesterol level of 60 to 180 mg per dL (1.55 to 4.66 mmol per L), a high-density lipoprotein (HDL) cholesterol level of less than 55 mg per dL (1.42 mmol per L), and a triglyceride level of less than 750 mg per dL (8.47 mmol per L). The mean follow-up period was 4.7 years. The primary outcome was a composite of the first occurrence of a major fatal or nonfatal cardiovascular event (i.e., myocardial infarction or stroke). Baseline characteristics were similar between groups: 37 percent had experienced a previous cardiovascular event and 60 percent were taking a statin before enrollment.

Results: No difference was noted between groups with regard to the composite cardiovascular outcome (2.2 versus 2.4 percent annual incidence for the fibrate and placebo groups, respectively). However, analysis based on sex showed that fibrates might have a benefit in men (11.2 versus 13.3 percent incidence of the primary outcome in the fibrate versus placebo group during the entire study; $P = .01$), whereas the reverse occurred in women (9.1 versus 6.6 percent, respectively; $P = .01$). A nonsignificant trend toward benefit occurred overall in patients with a triglyceride level of 204 mg per dL (2.31 mmol per L) or more and an HDL level of 34 mg per dL (0.88 mmol per L) or less. No differences were noted in most secondary outcomes (i.e., congestive heart failure, all-cause mortality, or separate analyses of myocardial infarction or stroke).

Conclusion: The authors conclude that, compared with simvastatin monotherapy, adding fenofibrate does not reduce the risk of cardiovascular events in patients with type 2 diabetes. This combination is not supported to prevent cardiovascular risk in most patients with type 2 diabetes; however, a small potential benefit occurred in men using both agents.

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Source: The ACCORD Study Group, Ginsberg HN, et al. Effects of combination lipid therapy in type 2 diabetes mellitus [published correction appears in *N Engl J Med.* 2010;362(18):1748]. *N Engl J Med.* April 29, 2010;362(17):1563-1574.

Effects of Intensive Blood Pressure Control in Patients with Diabetes Mellitus

Background: The risk of cardiovascular disease rises as systolic blood pressure increases in patients with type 2 diabetes mellitus. Current guidelines from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure advise lowering systolic blood pressure to less than 130 mm Hg in patients with diabetes; however, there is little evidence to indicate that this improves clinical outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group evaluated the effects of intensive blood pressure control on cardiovascular events in patients with diabetes.

The Study: A total of 4,733 patients with type 2 diabetes were randomized to one of two blood pressure control groups: intensive therapy (target systolic blood pressure of less than 120 mm Hg) or a control group (target systolic blood pressure of less than 140 mm Hg). Patients

were followed for an average of 4.7 years. Blood pressure was managed using standard antihypertensive agents, but no specific strategy was enforced. The primary outcome was a composite of the first occurrence of a major fatal or nonfatal cardiovascular event (i.e., myocardial infarction or stroke). Various secondary outcomes (i.e., separate assessments for myocardial infarction, stroke, congestive heart failure, and all-cause mortality) also were evaluated.

Results: Baseline traits between groups were similar, including initial blood pressure and incidence of previous cardiovascular events. No significant difference in the primary outcome was noted between groups, despite the intensive treatment group maintaining significantly lower blood pressure than the control group (mean blood pressures: 119.3/64.4 mm Hg versus 133.5/70.5 mm Hg, respectively). Most secondary outcomes showed no differences between groups, including all-cause or cardiovascular-related mortality, congestive heart failure, or myocardial infarction. However, the intensive therapy group had a lower incidence of total strokes than did the control group (0.32 versus 0.53 percent per year, respectively; hazard ratio = 0.59; $P = .01$) and nonfatal strokes (0.30 versus 0.47 percent per year, respectively; hazard ratio = 0.63; $P = .03$).

Conclusion: The authors conclude that a more stringent blood pressure goal for patients with type 2 diabetes does not significantly reduce the primary cardiovascular outcome or most secondary outcomes compared with standard blood pressure goals. In this study, the number of total and nonfatal strokes was lower in the intensive therapy group, although the clinical benefit was limited (number needed to treat = 89 for five years to prevent one stroke).

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Source: The ACCORD Study Group, Cushman WC, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* April 29, 2010;362(17):1575-1585.

High Doses of B Vitamins May Worsen Diabetic Nephropathy

Background: Diabetic nephropathy resulting in end-stage renal disease is a reality for more than 44 percent of patients with diabetes mellitus. In addition to the medical challenges, treatment of nephropathy causes a serious financial burden, costing the United States more than $10 billion annually. Observational studies have suggested a relationship between elevated plasma homocysteine levels and the risk of developing diabetic nephropathy. House and colleagues hypothesized that B-vitamin therapy, which has been shown to lower homocysteine levels, would slow diabetic nephropathy and prevent subsequent vascular events, such as myocardial infarction and stroke.

The Study: The DIVINe (Diabetic Intervention with Vitamins to Improve Nephropathy) study, a multicenter, randomized, double-blind, placebo-controlled trial of patients with types 1 or 2 diabetes, was conducted between May 2001 and July 2007. Adults with diabetes and known renal disease were eligible, although those with stages 4 or 5 renal failure, expected survival of less than three years, creatinine clearance of less than 30 mL per minute per 1.73 m^2 (0.50 mL per second per m^2), or those already on dialysis were excluded. In all, 238 patients were randomized to receive a daily B-vitamin supplement tablet that included folic acid (2.5 mg), vitamin B_6 (25 mg), and vitamin B_{12} (1 mg) or a matching placebo. Follow-up occurred at six-month intervals for up to 36 months. Patients were permitted to take all other vitamin supplements but not additional doses of the B vitamins studied in the trial. A baseline glomerular filtration rate (GFR) and plasma homocysteine level were established for each patient, and levels were checked periodically throughout the study. The primary end point was progression of nephropathy, as measured by change in GFR. Secondary end points included dialysis, occurrence of vascular events, all-cause mortality, cognitive decline, and amputation.

Results: Although the initial trial size of 286 patients was designed to provide 80 percent power to detect a 25 percent reduction in GFR, the authors stopped enrollment after 252 patients when it was noted that the intervention group's GFR was falling faster than the predicted rate of the placebo group. The data and safety monitoring committee determined that continuing the study would not likely yield a significant benefit in the primary end point. Although the intervention group had significantly lower homocysteine levels than the placebo group at 36 months, the B-vitamin group had a statistically significant decrease in mean GFR (16.5 mL per minute per 1.73 m^2 [0.28 mL per second per m^2]) compared with placebo (10.7 mL per minute per m^2 [0.18 mL per second per m^2]; $P = .02$). Equal numbers of patients progressed to dialysis in each group, but patients in the B-vitamin group had higher rates of myocardial infarction, stroke, revascularization, and all-cause mortality. None of the individual events reached statistical significance, but the overall rate of secondary outcomes was statistically significant ($P = .04$).

Conclusion: The authors conclude that supplementation with high doses of B vitamins lowers plasma ▶

homocysteine levels but worsens diabetic nephropathy and increases the risk of cerebrovascular and cardiovascular events in patients with diabetes. Other nonvitamin methods of reducing plasma homocysteine levels should be investigated.

MARY ANN MAURER, DO

Source: House AA, et al. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. *JAMA.* April 28, 2010;303(16):1603-1609.

Oral Antidiabetic Drugs Similarly Effective When Added to Metformin

Background: The American Diabetes Association (ADA) recommends lifestyle modification and metformin (Glucophage) for primary treatment of type 2 diabetes mellitus. Most patients, however, will eventually require additional antidiabetic medication to reach treatment goals. The ADA recommends the use of sulfonylureas or insulin if an additional medication is needed. Other categories of antidiabetic medications, including thiazolidinediones (e.g., pioglitazone [Actos]), glucagon-like peptide-1 (GLP-1) analogues, glinides, alpha-glucosidase inhibitors, and dipeptidyl-peptidase-4 (DPP-4) inhibitors are not supported by the ADA guidelines. To evaluate the effectiveness of these other drugs in combination with stable doses of metformin, Phung and colleagues constructed a mixed-treatment comparison meta-analysis.

The Study: The authors conducted a systematic search of Medline and Cochrane CENTRAL from 1950 through January 2010 to identify studies that (1) did not use insulin; (2) evaluated patients who had inadequate control on maximum-tolerated doses of metformin; (3) were parallel-design randomized controlled trials; (4) compared the addition of one antidiabetic drug to metformin with another antidiabetic drug or with placebo; (5) followed patients for 12 to 52 weeks after randomization; and (6) reported A1C levels. Validity was assessed for each study with the Jadad scale to measure inherent bias. The end points measured included the mean change in A1C level, number of patients meeting the A1C goal of less than 7 percent, incidence of weight loss, and incidence of hypoglycemic episodes.

Results: Of the 45 full-text articles reviewed, 31 (representing 27 randomized controlled trials) were eligible for inclusion. When added to metformin, each class of antidiabetic medication showed statistically significant reductions in A1C level compared with placebo. Overall, each medication class was more effective than placebo in achieving the A1C goal, with some subgroup differences. Sulfonylureas, glinides, thiazolidinediones, and DPP-4 inhibitors were effective regardless of the starting A1C level; alpha-glucosidase inhibitors and GLP-1 analogues were also effective if the starting A1C level was 8 percent or more. Similarly, sulfonylureas, glinides, thiazolidinediones, and DPP-4 inhibitors were effective regardless of the study duration, whereas the alpha-glucosidase inhibitors and GLP-1 analogues were significantly more effective than placebo only in studies lasting longer than 24 weeks.

The adverse effect profiles were different among classes. Sulfonylureas, glinides, and thiazolidinediones were associated with an approximate 4.4-lb (2.0-kg) weight gain. Alpha-glucosidase inhibitors and DPP-4 inhibitors were weight-neutral, and the GLP-1 analogues were associated with statistically significant weight loss (approximately 3.8 lb [1.7 kg]). Hypoglycemic events also varied; sulfonylureas and glinides were associated with increased risk of hypoglycemia, whereas the other classes did not show any hypoglycemic tendencies compared with placebo.

Conclusion: The authors conclude that all classes of noninsulin antidiabetic drugs effectively lower A1C levels when used as second-line treatment with metformin. Weight gain, risk of hypoglycemia, cost, and other comorbidities should help determine which drug to select.

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Source: Phung OJ, et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA.* April 14, 2010;303(14):1410-1418. ■