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Target Audience

This educational activity is designed for primary care physicians, internal medicine specialists, endocrinologists, diabetologists, cardiologists, and other healthcare professionals involved in the care and management of patients with type 2 diabetes, insulin resistance, and cardiovascular disease.

Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Identify patients with insulin resistance, type 2 diabetes, and/or cardiovascular disease
- Select the most appropriate therapeutic regimen for patients with type 2 diabetes and its macrovascular and microvascular complications
- Identify risk factors for cardiovascular disease in patients with type 2 diabetes and select an appropriate therapeutic regimen

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Grantor

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A Meta-analysis of the Effects of Therapy With Inhibitors of the Renin-Angiotensin System on Proteinuria in Patients With Renal Disease

Proteinuria is linked to an increased risk for progression of chronic kidney disease and the development of end-stage renal failure. Both angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce proteinuria. However, results of the antiproteinuric action of ARBs are variable. In addition, the relative effects of ARBs as compared with those of ACEIs, or with their combined administration, on proteinuria are not well understood. To address these questions, Kunz and colleagues conducted a systematic review and meta-analysis of the effects of monotherapy and combination therapy with ARBs, ACEIs, and other antihypertensive agents on urinary protein excretion in patients with nephropathy.

Studies in MEDLINE and the Cochrane Library Central Register of Controlled Trials (January 1990 to September 2006), reference lists, and expert contacts were used to search for potentially relevant randomized controlled trials (RCTs) of ARBs versus placebo, ACEIs, calcium-channel blockers (CCBs), or the combination of ARBs and ACEIs involving patients with microalbuminuria or proteinuria. Eligible patients, with or without diabetes, had data on urinary protein excretion available from baseline and from months 1 to 12. Data were extracted from studies that were independently searched and abstracted by 2 investigators.

Forty-nine RCTs involving 6,181 participants were selected for evaluation. Of these RCTs, 72 comparisons with 1 to 4 months of follow-up and 38 comparisons with 5 to 12 months of follow-up were performed. The authors found that ARBs reduced proteinuria when compared with placebo at a ratio of means of 0.57 (95% confidence interval [CI], 0.47 to 0.68) for 1 to 4 months of treatment and 0.66 (CI, 0.63 to 0.69) for 5 to 12 months. Both ARBs and CCBs decreased blood pressure to a similar degree; however, ARBs demonstrated a greater antiproteinuric action than CCBs, with a ratio of means of 0.69 (CI, 0.62 to 0.77) for 1 to 4

months and 0.62 (CI, 0.55 to 0.70) for 5 to 12 months of treatment.

ARBs and ACEIs reduced proteinuria to a similar extent during both 1 to 4 months and 5 to 12 months of treatment. The combination of ARBs and ACEIs further reduced proteinuria beyond the level achieved with either agent alone. The ratio of means for combination therapy vs ARBs was 0.76 (CI, 0.68 to 0.85) during 1 to 4 months and 0.75 (CI, 0.61 to 0.92) during 5 to 12 months; and for combination therapy vs ACEIs, the ratio of means was 0.78 (CI, 0.72 to 0.84) during 1 to 4 months and 0.82 (CI, 0.67 to 1.01) during 5 to 12 months. Additionally, the antiproteinuric effect was consistent across clinical subgroups, such as patients with microalbuminuria and proteinuria and patients with diabetic and nondiabetic nephropathy.

The investigators indicated that the comprehensive search, the interpretation of analyses, and the consistency and congruity of the results are among the strengths of their systematic review and meta-analysis. Limitations for this study included the small sample size of most studies, the unreliable data on adverse effects, and the varied methodological qualities of some studies.

Kunz and associates concluded that monotherapy with ARBs and ACEIs achieves similar antiproteinuric effects in patients with microalbuminuria and proteinuria regardless of the degree and cause of renal disease. Concomitant administration with an ARB and an ACEI, at usual doses, is more effective in reducing proteinuria than either drug alone. Uncertainty regarding the risk for adverse effects and the benefits considered important to patients limits the implications of these findings for clinical practice.

Kunz R et al. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med.* 2008;148(1):30-48.

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COMMENTARY

VIVIAN FONSECA, MD, Professor of Medicine and Pharmacology, Tullis Tulane Alumni Chair in Diabetes, Tulane University School of Medicine, and Chief, Section of Endocrinology, Tulane University Health Sciences Center, New Orleans, Louisiana.

This meta-analysis confirms that angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) have equal potency in reducing proteinuria and are superior in this respect to other antihypertensive agents—possibly due to their specific intra-renal effects. These findings are no surprise to clinicians dealing with diabetic nephropathy who have long used these drugs for this purpose based on well-conducted studies.

In addition, this analysis shows that the combination of ARBs and ACEIs leads to greater reductions in proteinuria than either drug alone. Again, this finding is no surprise, as several other studies have demonstrated. The authors point to the limitation of the studies used in their analyses because they were of relatively short duration and do not provide data on outcomes that “matter to patients.” In this respect, this conclusion is a bit premature because such trials are ongoing. The ONTARGET and TRANSCEND studies are designed to determine whether the ARB telmisartan is similar or superior to ramipril in the reduction of cardiovascular events in patients with established cardiovascular disease or diabetes experiencing target organ damage. The ONTARGET study has enrolled over 20,000 patients and TRANSCEND over 5,000 subjects. These studies completed recruitment in 2004 and are due to complete follow-up and report the results in 2008. These studies will provide valuable comparative data on the efficacy of ARBs and ACEIs and their combination in patients at high risk for cardiovascular events.

It is important to recognize that patients with proteinuria are a “high-risk” group and aggressive therapy is warranted. Those who have persistent proteinuria despite blockade of the renin-angiotensin system have a poor prognosis.

Gastric Banding Surgery Leads to Type 2 Diabetes Remission in Obese Patients

Several observational studies have suggested that using bariatric surgery to achieve significant sustained weight loss may be an effective treatment for type 2 diabetes, but there have been no known randomized controlled trials examining this possibility. Dixon and colleagues conducted a 2-year, randomized, controlled trial involving 60 obese patients recently diagnosed as having type 2 diabetes (<2 years) to compare the effects of weight loss from laparoscopic adjustable gastric banding (LAGB) with those of weight loss from conventional therapy.

The patients, studied at an Australian obesity research center, were between the ages of 20 and 60 years with a body mass index (BMI) >30 and <40 kg/m² (mean 37.1) and no evidence of renal impairment or diabetic retinopathy. Exclusions included previous bariatric surgery, type 1 diabetes, a recent major vascular event, or other contraindications. Each patient was assessed by a dietitian, a general physician, and an endocrinologist specializing in diabetes. The healthcare team suggested changes intended to maximize current diabetes management during a run-in period of 3 months or more, with the endocrinologist choosing the proper time for randomization.

Patients were randomly assigned to 2 treatment groups (n=30 each group), the conventional therapy group and the bariatric surgery group. The conventional group received best-practice treatment, education, and follow-up, which included open access to a healthcare professional, regular health visits every 6 weeks during the 2-year program, an individually designed lifestyle modification, including diet and exercise programs, as well as pharmaceutical therapy as needed. The surgery group received the same therapy as the conventional group in addition to placement of a LAG band via the pars flaccida technique by 1 of 2 surgeons

within 1 month of randomization. Patient progress was reviewed by the surgery team every 4 to 6 weeks throughout the study and band volume adjustments were made as needed based on standard clinical criteria.

Primary endpoint was the proportion of participants achieving remission of their diabetes, defined as fasting plasma glucose levels <126 mg/dL and A1C values <6.2% without use of insulin or oral hypoglycemics. Secondary outcomes included percentage changes in measures of blood pressure, weight, A1C, fasting lipids, and waist circumference.

At the end of the 2-year program, 29 (97%) of the surgery group and 26 (87%) of the conventional group completed the trial. Twenty-two of 29 (76%) in the surgery group and 4 of 26 (15%) in the conventional group achieved diabetes remission. (Including the patients who withdrew prior to completion, 22 of 30 in the surgery group and 4 of 30 in the conventional group achieved remission; $P<0.001$.) Estimating the most conservative conclusion with the 1 surgical noncompleter not achieving remission and the 4 conventional noncompleters achieving remission, the results (22/30 [73%] and 8/30 [27%], respectively) remained significant ($P<0.001$).

Greater percentage of weight loss ($R^2=0.46$; $P<0.001$) and, to a lesser degree, lower baseline A1C ($R^2=0.50$ for both; $P<0.001$) were the only variables independently associated with remission. Only 4 of 34 patients (12%) who lost <10% of body weight achieved remission after 2 years, and only 4 of 26 (15%) who lost >10% of body weight did not achieve remission. The surgical group achieved a mean body weight loss of 20.0% (SD, 9.4%) after 2 years versus 1.4% (SD, 4.9%) in the conventional group ($P<0.001$), representing a loss of excess weight equalling 62.5% and 4.3%, respectively (using a BMI of

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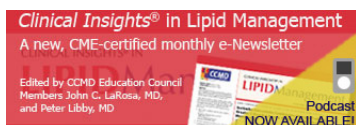
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Gastric Banding Surgery Leads to Type 2 Diabetes Remission in Obese Patients

Continued

25 as ideal weight). Mean BMI dropped from 36.9 to 29.5 in the surgical group and 37.1 to 36.6 in the conventional group.

Compared with the conventional therapy group, the surgical group had significant reductions in A1C levels, use of metformin, use of other hypoglycemic agents ($P=0.006$), and use of antihypertensive drugs ($P=0.005$), as well as significantly greater improvements in insulin sensitivity, triglyceride levels ($P=0.02$), HDL-C levels, and waist circumference ($P<0.001$ for each measurement unless otherwise noted). The authors note that changes in secondary outcomes measures are for hypothesis-generating only because the study was not powered for a full examination of these measures. Adverse events were minor in both groups.

The study had several limitations. First, restricting the study to patients with recently (<2 years) diagnosed type 2 diabetes limits the application of these results to patients with a longer duration of diabetes. Second, the LAGB surgical team in this study was highly experi-

enced in the technique; studies have shown an inverse relationship between the experience of LAGB surgeons and the occurrence of postoperative patient complications. Third, the study was not designed to measure such outcomes as cardiovascular events or mortality and follow-up was limited to 2 years, which limited the long-term extrapolations of the results.

The authors concluded that greater weight loss from LAGB resulted in diabetes remission and other metabolic improvements in the majority of obese patients with recently diagnosed type 2 diabetes. They suggested the need for larger, longer studies to better determine long-term efficacy.

Dixon JB et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;299(3):316-323.

Oral Glucose Tolerance Test: A Reliable Tool for Early Detection of Glucose Abnormalities in Patients With Acute Myocardial Infarction

High prevalence of previously undetected glucose abnormalities was observed in patients with acute myocardial infarction (AMI), as reported by the GAMI (Glucose tolerance in Acute Myocardial Infarction) study. Postinfarction patients with newly detected disturbed glucose metabolism were shown at an increased risk for cardiovascular morbidity and mortality. These observations suggested the importance of early diagnosis of glucose metabolism in patients with AMI.

In the present study, Wallander and colleagues evaluated long-term reliability of early classification of glucose abnormalities in patients with AMI using repeated oral glucose tolerance tests (OGTTs). Patients with AMI but without previously detected type 2 diabetes were recruited according to the inclusion criteria set by the GAMI study. A standard OGTT (75-g glucose in 200 mL water) was performed by measuring capillary whole-blood glucose. A glucometabolic OGTT-based classification—normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or type 2 diabetes—was obtained from 122 patients. Classification was performed on 3 occasions: before hospital discharge and at 3 and 12 months after discharge.

The investigators found that, at the time of hospital discharge, 34% of the 122 patients were classified as having NGT, 31% had IGT, and 34% had type 2 diabetes. Among all patients classified with type 2 diabetes at discharge, 93% were

still classified with type 2 diabetes ($n=27$) or IGT ($n=12$) after 12 months. Of the patients classified as having NGT at discharge, 60% remained at NGT after 12 months. Agreement among the OGTT measurements from discharge to 3 months and from 3 to 12 months were as follows: $\kappa=0.35$ ($P<0.001$) and $\kappa=0.43$ ($P<0.001$), respectively, with $\kappa=1$ for complete agreement.

Patients who had progressed from NGT at discharge to IGT or type 2 diabetes after 12 months had significantly higher A1C levels at discharge. Patients originally classified with type 2 diabetes who remained diabetic after 12 months had a more diabetic phenotype at discharge, with higher levels of A1C and triglycerides, and homeostasis model assessment of insulin resistance, and decreased β -cell secretion as measured by adjusted insulinogenic index.

These authors concluded that the outcome of an OGTT performed in patients with AMI at hospital discharge is a reliable measure of a patient's long-term glucometabolic state.

Wallander M et al. Oral glucose tolerance test: a reliable tool for early detection of glucose abnormalities in patients with acute myocardial infarction in clinical practice: a report on repeated oral glucose tolerance tests from the GAMI study. *Diabetes Care*. 2008;31(1):36-38.



Clinical Insights® in Diabetes Post-Test January 2008

1. In a recent study examining treatment of proteinuria with inhibitors of the renin-angiotensin system, which of the following was NOT a conclusion of the authors?
 - a) Calcium channel blockers (CCBs) had a greater antiproteinuric effect than angiotensin-converting enzyme inhibitors (ACEIs)
 - b) Angiotensin receptor blockers (ARBs) and ACEIs showed similar antiproteinuric effects as monotherapies
 - c) Both ARBs and CCBs decreased blood pressure to a similar degree
 - d) Concomitant doses of both ARBs and ACEIs are more effective in reducing proteinuria than either drug alone

2. Which of the following was NOT a result of a 2-year study comparing conventional therapy with gastric banding surgery in a group of patients with type 2 diabetes of 2 years or less?
 - a) Approximately three-quarters of the surgery group experienced diabetes remission
 - b) Lower baseline A1C was the predominant variable associated with remission
 - c) The surgery group lost a mean of 20% of total body weight
 - d) Greater percentage of weight loss was the predominant variable associated with remission

3. A study of patients with a recent acute myocardial infarction found that using oral glucose tolerance tests at hospital discharge
 - a) Was a reliable measure of a patient's long-term glucometabolic state
 - b) Was not a reliable measure of a patient's long-term glucometabolic state
 - c) Was a reliable measure for patients with type 2 diabetes, but not for others
 - d) Was a reliable measure for short-term metabolic status, but not long-term

ANSWER KEY

1. a) Calcium channel blockers (CCBs) had a greater antiproteinuric effect than angiotensin-converting enzyme inhibitors (ACEIs). CCBs had a lesser effect than ACEIs or angiotensin-receptor blockers in reducing proteinuria.

2. b) Lower baseline A1C was the predominant variable associated with remission. Although lower baseline A1C was 1 of 2 variables associated with remission, greater percentage of weight loss was the predominant variable associated with remission.

3. a) Was a reliable measure of a patient's long-term glucometabolic state. Among all patients measured as having type 2 diabetes at discharge, 93% were still classified with type 2 diabetes (n=27) or IGT (n=12) after 12 months.

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Clinical Insights® in Diabetes is co-edited by NDEI faculty members Mayer B. Davidson, MD, and Silvio E. Inzucchi, MD.

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