Evidence-Based Practice

Answering clinical questions with the best sources

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TRANSFORMING PRACTICE

Surgical treatment for morbid obesity

Evidence points to improved patient-important outcomes

Summary of evidence

- Patients undergoing various bariatric surgical procedures lost an average of 61.2% of their excess weight (varying from 47.5% for gastric banding to 70.1% for biliopancreatic diversion or duodenal switch procedures)
- Perioperative mortality was relatively low (varying from 0.1% for banding, 0.5% for bypass, to 1.1% for biliopancreatic diversion or duodenal switch)
- Most patients had resolution of or improvement in comorbid conditions; most notably, resolution of diabetes was 98.9% for biliopancreatic diversion or duodenal switch, 83.7% for gastric bypass, 71.6% for gastropasty, and 47.9% for gastric banding

Once an unusual procedure performed only in a few academic centers, surgical treatment for morbid obesity is now widely available. Its use has skyrocketed along with the US obesity epidemic and, the best news, good evidence shows that morbidly obese patients are now achieving outstanding outcomes from surgery. In a recently published meta-analysis, bariatric surgery led to the loss of more than 60% of body weight, was associated with resolution of comorbidities (hypertension, diabetes, hyperlipidemia, obstructive sleep apnea) in more than 75% of patients, and added an average of 7 years of life.\(^1\)

Family physicians and general internists need to know the criteria for referral, provide their patients with information to motivate them to consider this option, and understand the special needs and potential complications for long-term care of patients after bariatric surgery. Herein we review the evidence supporting surgical treatment of morbid obesity as well as complications.

continued
Definitions

Current accepted definitions of overweight are based on the body mass index (BMI). The BMI is defined as body weight (in kilograms) divided by height (in meters) squared. Table 1 shows classifications of weight according to BMI. "Excess weight" refers to the difference between the patient’s actual baseline weight and his or her optimal body weight.

In 1998, the National Heart, Lung, and Blood Institute Consensus Panel recommended surgery for weight loss as an option for selected patients with clinically severe obesity. Severe obesity was defined as BMI of 40 kg/m² or higher, or BMI between 35 and 40 kg/m² with comorbid conditions including poorly controlled hypertension, type 2 diabetes mellitus, obstructive sleep apnea, or coronary artery disease. The panel also recommended that patients be required to be free from substance abuse, major psychosis, and untreated depression.

Types of surgical procedures

The meta-analysis divided the surgical procedures types into 5 broader categories. Most procedures restrict the volume capacity of the stomach and modify the functional anatomy of the stomach (gastroplasty), bypass portions of the gastrointestinal tract, or divert the contents of the biliopancreatic segment of the duodenum to the distal small bowel. The 5 categories of bariatric surgery assessed were:

- **Gastric banding**: Included adjustable and nonadjustable gastric banding procedures, without gastroplasty, bypass, or diversion component
- **Gastric bypass**: Principally the Roux-en-Y gastric bypass procedure (includes banding) or any mixed procedure that included bypass (bypass plus banding, gastroplasty, or biliopancreatic diversion)
- **Gastroplasty**: Principally vertical banding with gastroplasty
- **Biliopancreatic diversion or duodenal switch**: Included a variety of modifications
- **Other**: Included all other bariatric procedures, as well as nonspecified procedures

Meta-analysis

The primary outcomes of interest for this meta-analysis were rates of resolution or improvement in 4 predefined comorbidities: type 2 diabetes mellitus, hyperlipidemia, hypertension, and obstructive sleep apnea. Criteria for including an individual study in the meta-analysis included a minimum of 10 patients who underwent bariatric surgery, publication date between 1990 and 2003, and data on at least 1 of the predefined comorbidities. Clinical trials and case series were included.

Secondary outcomes of interest were perioperative mortality, defined as death from any cause within 30 days of surgery, and weight loss. "Resolution" of the primary outcomes was defined as the disappearance of the comorbid condition, or a condition for which therapy was no longer required.

A total of 136 studies that enrolled 22,094 patients met inclusion criteria. Of these, only 5 studies (621 patients) were randomized controlled trials (RCTs); 28 (4,613 patients) used nonrandomly assigned control groups and 101 studies (16,860 patients) were case series. The mean age was 39 years (range 16–63), the mean BMI at baseline was 46 (range 32–68), and most patients were female (72%). The age and baseline BMIs of patients were similar across surgical procedure types.

Findings

Including all studies, patients lost an average of 61.2% of their excess weight (95% confidence interval [CI], 58.1%–64.4%). The range of percentage of excess weight lost was from 47.5% (95% CI, 40.7%–54.2%) for gastric banding to 70.1% (95% CI, 66.3%–73.9%) for biliopancreatic diversion or duodenal switch procedures. Perioperative mortality was relatively low, and varied according to procedure type (banding 0.1%, bypass 0.5%, biliopancreatic diversion or duodenal switch 1.1%). Table 2 shows the resolution or improvement rates for the comorbid conditions of interest from the combined data.

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**Table 1**

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Classification</th>
</tr>
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<tr>
<td>18.5–25</td>
<td>Optimal</td>
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<tr>
<td>25–30</td>
<td>Overweight</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Obese</td>
</tr>
<tr>
<td>40–50</td>
<td>Morbidly obese</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Superobese</td>
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</table>
What is the best agent for preventing oral herpes?

Valacyclovir 500 mg once daily reduces recurrence rate of herpes labialis, but the magnitude of the benefit is small. Sunscreen applied to the lips reduced recurrence rates of herpes labialis significantly among college students exposed to ultraviolet (UV) light in a laboratory setting. Although sunscreen has not been tested in natural conditions it may well be beneficial and is not harmful.

Pooled results from patients with a history of frequent outbreaks of recurrent herpes labialis (≥4 attacks per year) enrolled in 2 identical randomized controlled trials (RCTs) showed that the oral valacyclovir group (500 mg once daily for 16 weeks) had a 38% rate of recurrence during the 4-month study period, and mean time to first recurrence of 13.1 weeks. Corresponding rate and duration for the placebo group were 60% (NNT=5; \(P=0.041\)) and 9.6 weeks (\(P=0.016\)), respectively.

In a study of 147 skiers with a history of sun-induced recurrent herpes labialis, participants were randomly assigned to receive either acyclovir 400 mg orally twice daily beginning 12 hours before sunlight exposure or placebo. The rate of recurrence in the acyclovir group was lower (5% vs 26% in the placebo group; NNT=5; \(P<0.05\)). However a subsequent study of similar design (239 skiers with history of recurrent herpes labialis; 800 mg acyclovir twice daily beginning the day before sun exposure vs placebo) showed no difference in recurrence rates (23% with acyclovir vs 21% with placebo; \(P=0.92\)).

Topical sunscreen may also be beneficial, but the studies done to date for this intervention have been limited to experimental situations. In both of these studies, patients were intentionally exposed to doses of UV radiation in the lab, and were found to have significant reduction in the induction of recurrent herpes labialis when sunscreen was used compared to placebo. The value of this finding in clinical practice is uncertain.

When patients are planning to be in the sun for prolonged periods, sunscreen use is prudent whether or not they have herpes labialis. [Strength of recommendation (SOR): C, based on laboratory experiment] Valacyclovir is probably not warranted in patients with episodes of herpes labialis that recur fewer than 4 times per year. For those with frequent recurrences (>4 times a year), or for whom the pain or cosmetic concerns are particularly severe, a trial of oral valacyclovir may be warranted. [SOR: A, based on well-done RCT] Patients need to be informed of the modest effect size and that the cost of such treatment is high. The cost of 500 mg oral valacyclovir twice daily for 16 weeks at the local pharmacy is approximately $1,113.70, although drug prices vary remarkably these days (University of Missouri, Columbia Hospital and Clinics outpatient pharmacy; December 20, 2004).

What is the best agent for treating oral herpes?

The evidence shows that the best treatment is oral acyclovir, 400 mg taken 5 times daily, which reduces duration of symptoms by a mean of 4.4 days. [SOR: A, based on well-done RCT] However, surprisingly few antiviral regimens have been evaluated for the acute treatment of herpes labialis.

ORAL ANTIVIRALS

One RCT found that for 174 patients with a history of recurrent herpes labialis, symptoms lasted for an average of 4.4 days less for those taking 400
mg acyclovir 5 times daily for 5 days than for those taking placebo (8.1 vs 12.5 days; \( P = .002 \)).

Patients in this study were instructed to start treatment “at the first sign of symptoms.” In a RCT of similar design, however, no such benefit was found. A total of 149 patients were assigned to either 200 mg acyclovir 5 times daily for 5 days or placebo within 12 hours of the onset of symptoms. No significant differences were noted with respect to the outcomes of pain or lesion duration. This lack of difference may have been due to the low dose of antiviral medication used.

More recent studies of high-dose, short-duration valacyclovir show modest benefit. The results of 2 RCTs published in a single article in 2003 demonstrated that for patients who take either 1- or 2-day courses of high-dose valacyclovir (2 g twice daily for 1 day, or 2 g taken twice daily for 1 day, followed by 1 g twice daily for the second day) had reductions in duration of the episodes by 0.5 (\( P = .009 \)) to 1.0 (\( P = .001 \)) days, respectively.

### TOPICAL ANTIVIRALS

*Clinical Evidence* reports on 5 trials that studied the effect of topical antivirals for the treatment of recurrent herpes labialis lesions. Although some studies reported shorter duration of pain among patients using active drug versus placebo, the effect size was small. The range of decrease in pain duration in the 5 studies ranged from about 1 to 12 hours. Among the 10 trials that reported on time to complete healing as an outcome, again, the effect was variable and small. The shortened duration to complete healing in the active treatment groups amounted to a range of 6 hours to 2 days, with most showing reduction time of less than 1 day.


### What is the role of herpes virus serology in sexually transmitted disease screening?

The use of viral serology has no role as a screening tool for identification of asymptomatic infected individuals for herpes simplex virus (HSV). The US Preventive Services Task Force (USPSTF) recommends against the use of surveillance for herpes infections in asymptomatic individuals. The USPSTF, The American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the Canadian Task Force on the Periodic Health Examination, and the Infectious Disease Society of America all recommend against surveillance for herpes infections in asymptomatic pregnant women.

Approximately 16% of the US adult population is seropositive for HSV 2. The vast majority of these individuals are asymptomatic. Even though current commercially available serologic tests for HSV have sensitivities and specificities of about 95% with a low prevalence population (such as 16%), 30% to 40% of individuals who test positive would be wrongly diagnosed as being infected. Even in high-prevalence populations, the false-positive rate would be about 10%.

There is no evidence demonstrating effective means of preventing transmission of HSV 2, so making false-positive diagnoses cannot be justified. One study of 144 couples with 1 partner having recurrent genital herpes and the other partner with a seronegative status evaluated the impact of recommendations for avoiding skin-to-skin contact during times of active lesions. Couples who used barrier contraception did not have fewer episodes of the herpes transmission to the previously uninfected individual.

Until it is demonstrated that some benefit would be derived from such knowledge, routine testing for HSV infection in asymptomatic individuals is not recommended.

[SOR: B, based on prevalence studies and 1 non-randomized trial]

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What behavioral interventions are safe and effective in treating obesity?

No behavioral interventions have been shown to lead to meaningful, sustained weight loss.

A systematic review published in 1998 (search date 1997) found 3 RCTs that assessed the effect of adding behavioral interventions to recommendations for low or very low calorie diets. All 3 showed that the patients receiving behavioral counseling had either more weight loss or less weight gain than patients who had dietary counseling alone. However, in the 2 trials that reported 5-year outcomes, these differences did not persist. A second systematic review from 1999 found no RCTs that demonstrated sustained benefit with respect to weight loss for patients receiving behavioral therapy in addition to dietary counseling. A subsequent RCT, published in 2003, showed some benefit from the addition of cognitive behavioral therapy (CBT) to usual care in a primary care setting. In this study, 122 obese subjects (body mass index > 30 kg/m²; mean age 45.2 years) were randomized to receive either 16 90-minute sessions of group CBT or usual care. Twelve months after the end of therapy, patients who received CBT had lost 4 pounds, compared to a 0.5-pound weight loss in the control group ($P<.001$).

Behavioral interventions are therefore unlikely to result in significant, prolonged weight loss. Particularly for morbidly obese patients (see Transforming Practice article in this issue), more aggressive treatment is required. [SOR: A, based on multiple RCTs]


Is humidified oxygen effective for treating children with croup?

Humidified oxygen has not been shown to be effective for treating children with croup, although we found only 1 trial addressing this question.

In that trial, 71 children, aged 3 months to 6 years, presenting to the emergency department with moderate croup were randomly assigned to receive humidified oxygen mist or no mist. All patients received a dose of oral dexamethasone (0.6 mg/kg). Other treatments, such as racemic epinephrine could be prescribed at the discretion of the treating physician. Baseline croup scores were obtained (initially 2–7), and repeated every 30 minutes for up to 2 hours, or until the score was less than 2. The 2 treatment groups had similar characteristics at baseline, and the initial median croup score was 4 for both groups. The outcome of interest was change in croup score from baseline for each of the follow-up time intervals.

No significant differences were noted in the changes of croup scores for any of the time points studied ($P=.39$). Nor were there significant differences in improvement of oxygen saturation, heart rate, or respiratory rate at any of the assessment times. [SOR: B, based on 1 RCT]


Are corticosteroids effective for treating children with mild-to-moderate croup?

Corticosteroids reduce length of stay in emergency departments, reduce hospital admissions, reduce rate of return visits to emergency departments and improve clinical measures of croup severity. One oral dose of dexamethasone (0.6 mg/kg) is effective for mild croup (no stridor, no intercostals retractions).

One trial randomly assigned children who presented to the emergency room with croup, whose illness was not severe enough to warrant hospitalization, to receive either 0.15 mg/kg of oral dexamethasone or placebo prior to release. A total of 100 children (age range 4–122 months, 90% younger than 6) participated in the study, and the outcome of interest was what percentage would need subsequent medical contact for croup-related concerns. Parents of 96 of 100 of these children were contacted 7 to 10 days after the emergency room visit, and asked about whether any further medical attention had been sought for croup.

For patients receiving dexamethasone, none of the 50 children required further care, but for those receiving placebo, 8 of 50 (16%) were seen again.
for croup (absolute risk reduction 0.16, NNT to prevent the need for further croup-related care 7; \(P<.01\)). One of the children in the placebo group was admitted to the hospital.

In a systematic review (most recent update, August 2003) the authors identified 31 relevant studies that included 3,736 patients that compared the use of corticosteroids to placebo in children with croup. Studies were included regardless of croup severity. When the data from these studies were combined, significant benefit was found from the use of corticosteroids for multiple clinically important outcomes. A Westley score was used to measure clinical response. This is a 17-point croup severity score that includes assessment of air entry (2 points), stridor (2 points), intercostal retractions (3 points), cyanosis (5 points), and level of consciousness (5 points). At 6 hours, patients receiving corticosteroids did better than those receiving placebo, with a weighted mean difference of –1.2 points (95% confidence interval [CI] –1.6 to –0.8). At 12 hours the difference was –1.9 (–2.4 to –1.3). At 24 hours this improvement was no longer significant (–1.3; 95% CI, –2.7 to 0.2). The risk of having to have a return visit or readmission to the hospital was also reduced for the patients receiving corticosteroids (relative risk 0.50; 95% CI, 0.36 to 0.70), as was the length of stay in the emergency department or the hospital (weighted mean difference 12 hours; 95% CI, 5 to 19). Patients receiving corticosteroids also were found to require fewer epinephrine treatments (risk difference 10%; 1%–20%). [SOR: A, based on consistent RCTs]


Is racemic epinephrine effective for treating children with croup?

Multiple RCTs have demonstrated benefit from nebulized racemic epinephrine in children with moderately severe croup. This benefit is reflected in changes in croup scores from baseline.

A trial from 1994 randomized 54 children with mild-to-moderate croup to receive a nebulized solution containing 2.25% racemic epinephrine, or an identical solution without active drug. Children receiving epinephrine had a mean change from a baseline croup score (on a 15-point scale) of –2.7 compared with –1.1 with placebo (\(P=.003\)). Two other RCTs compared the use of nebulized racemic epinephrine delivered by intermittent positive-pressure breathing (IPPB) device, and found a similar benefit. In the first of these, 20 children with moderate-to-severe croup were treated with either 0.5 mL of nebulized 2.25% racemic epinephrine or placebo, delivered through IPPB. Croup scores were significantly improved in children receiving racemic epinephrine at 10 and 30 minutes, but this benefit was no longer seen at 120 minutes. In the second study, 14 children were randomized to receive either a weight-adjusted dose of 2.25% racemic epinephrine or placebo through IPPB. Again, children receiving epinephrine had better croup scores at 20 minutes than those receiving placebo, but the researchers also found that within 24 to 36 hours of admission, the clinical status of patients in the treatment group were not significantly different from those in the control group.

These consistent results from multiple RCTs show that epinephrine favorably affects the short-term clinical status of the patient, but that effect wears off within about 2 hours. This finding is particularly important with respect to management of moderate-to-severe croup in the emergency department. Significant improvement in a child’s respiratory status following treatment with racemic epinephrine should not be used as an indication that it is safe to send the child home. In fact, it is likely that within 2 hours, unless other interventions are made, that deterioration of respiratory function is likely to ensue. [SOR: A, based on consistent RCTs]


What are the best prevention strategies for "shin splints" in athletes?

The evidence we found to answer this question was weak, so we asked an expert to provide guidance (see the following Clinical Commentary).
He recommends a constant level of fitness and activity, gradual increases in intensity and duration of exercise, good shoes, and training on softer surfaces.

A systematic review of prevention of shin splints, published in 2002, yielded only 4 comparison studies. In each of 3 controlled RCTs involving a total of 6,163 military recruits, no change in the rate of shin splints was noted with the use of heel pads, boot inserts, heel-cord stretching exercises, graduated running programs, standard all-leather combat boots, or hot-weather canvas top boots for the 8- to 9-week training period. Of recruits in the control group, 65 of 1,151 (20.4%) had documented shin splints compared with 6 of 237 (12.8%) in the insert group (P<.05).

The quality of the studies cited by this review was poor. None reported adequate methods of randomization, whether blinding occurred, basic statistical testing methods or power calculations. In the second study cited, members of the intervention (canvas-top) group who were found to be noncompliant with the study protocol were moved to the control group for analysis, compromising random allocation and introducing possible confounding bias. The quality scores for these 4 trials ranged from 29 to 47 points (out of a possible 100).

Negative findings from poorly designed studies do not prove ineffectiveness. [SOR: B, based on a systematic review of low-quality studies] Currently, expert clinical experience is the best guide available (see Clinical Commentary).

Clinical Commentary

I recommend a consistent level of fitness and activity or gradual increases in intensity and duration using an appropriately staged training program to prevent most shin splints and other overuse injuries.

Diminishing the force of the impact for the foot by avoiding training on hard surfaces such as concrete is also important. Good supportive shoes are critical to cushion impact, especially for runners with hyperpronation or cavus feet. If shoes are visibly worn, or have just seen a lot miles, I recommend new shoes.

— Roy Henderson, MD, Director, Sports Medicine Fellowship, MacNeal Family Practice Residency Program, & Department of Family Medicine, The University of Chicago

CME CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Michigan State University, College of Human Medicine. Michigan State University, College of Human Medicine, is accredited by the ACCME to provide continuing medical education for physicians. Michigan State University, College of Human Medicine, designates this educational activity for a maximum of 3 hours in category 1 credit toward AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that he or she actually spent in the educational activity.

It is estimated that this educational activity will require 3 hours to complete.

The learning objectives of the Evidence-Based Practice newsletter are to become knowledgeable about evidence-based solutions to commonly encountered clinical problems, to understand how groundbreaking research is changing the practice of family medicine, and to become conversant with balanced appraisals of drugs that are currently being marketed to physicians and/or consumers.

The editors of this educational material may review studies that discuss commercial products or devices as well as the unapproved/investigative use of commercial products/devices. The editors of this educational material report that they do not have significant relationships that create, or may be perceived as creating, a conflict relating to this educational material.

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The percent of resolution or improvement for these conditions varied according to the surgical procedure. The most striking change was for resolution of diabetes: 98.9% for those undergoing biliopancreatic diversion or duodenal switch, 83.7% for gastric bypass, 71.6% for gastroplasty, and 47.9% for gastric banding.

As noted, only 5 of the studies in this analysis were RCTs. However, the findings of the RCTs were in the range of values for the overall meta-analysis. Another concern was that most studies (104 of 136) reported outcomes with less than 2 years of follow-up. Nevertheless, when analyzed separately, studies with follow-up of longer than 2 years had weight loss outcomes that did not differ significantly from those with less than 2 years of follow-up.

A 20-year study of bariatric surgery is in progress to determine long-term outcomes. Started in 1987, the Swedish Obese Subjects study (SOS) recruits obese subjects using BMI criteria, and will eventually enroll 2,000 matched pairs of subjects—one of each pair electing bariatric surgery and the other electing aggressive nonsurgical intervention. Each pair will be followed for 10 years and re-examined at 15 and 20 years.

By February 2000, 1,879 patient-pairs had been enrolled, and preliminary data have suggested that the benefits of weight loss and the resolution of diabetes persist at 8 years, but that the rates of hypertension may begin to converge. Nine-year follow-up in SOS revealed that the surgical group had a mortality rate of 9%, compared with 28% of those in the nonsurgical group. Most of the deaths were from cardiovascular causes.

LONG-TERM COMPLICATIONS

Multiple complications, some potentially serious, are associated with bariatric surgical procedures.

Dumping syndrome (postprandial sweating, weakness, hypoglycemia, general malaise) is fairly common but is rarely severe, and usually disappears as patients adapt to their bypass anatomy. Vitamin deficiency, which can occur as a result of any of the bariatric procedures, is found in 11% of individuals who undergo surgery that involves restriction plus bypass. Therefore, daily vitamin and mineral replacement therapy is essential for all patients who undergo these procedures.

Gallstones develop in 30% of patients who have a bypass procedure. Cholecystectomy requiring surgery has been reported by 27% of patients within 3 years. Prophylactic cholecystectomy is one approach to prevention. Another is the use of ursodiol, which has been shown to reduce gallstone formation at 6 months to only 2% in patients who undergo bypass surgery.

Surgical complications, such as stricture formation and the development of fistulas, also are important risks, but have become less common. Excess skin is noticeable in most patients after extreme weight loss. In addition to being cosmetically disturbing for some, excess skin can also be associated with ulcerations, infections, and even disturbance of ambulation. Surgical revision for these complications is often required.

REFERENCES


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<tr>
<th>Comorbid condition</th>
<th>Resolved (%)</th>
<th>Improved* (%)</th>
<th>Resolved or improved (%)</th>
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<td>Type 2 diabetes</td>
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<td>—</td>
<td>86.0</td>
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<td>Hyperlipidemia</td>
<td>—</td>
<td>70</td>
<td>—</td>
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<tr>
<td>Hypertension</td>
<td>61.7</td>
<td>—</td>
<td>78.5</td>
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<tr>
<td>Obstructive sleep</td>
<td>85.7</td>
<td>—</td>
<td>83.6</td>
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</tbody>
</table>

* Defined as normalization of laboratory values or reduction or discontinuation of medical therapy.

TABLE 2

Improvement or resolution of comorbidities after bariatric surgery
Clinical pharmacology of eplerenone

A new selective aldosterone antagonist shows efficacy without the side effects associated with nonselective agents

RAMINDER KUMAR, MD, Clinical Associate Professor, Department of Family Medicine, University of Chicago

Eplerenone (Inspra) is a new aldosterone antagonist. Compared with spironolactone, it has markedly increased selectivity for the aldosterone receptor and low binding for progesterone (<1%) and androgen receptors (0.1%). Therefore, eplerenone does not cause the gynecomastia or breast pain seen with spironolactone. Eplerenone is indicated in treatment of hypertension and in patients who have left ventricular dysfunction (LVD) plus congestive heart failure (CHF) or diabetes mellitus (DM) after a recent (3–14 days) myocardial infarction (MI).

LVD plus CHF or DM after recent MI

Aldosterone blockade prevents ventricular remodeling and collagen formation in patients with LVD after acute MI. In a large, multicenter, international, randomized, double-blind, placebo-controlled trial 6,632 patients were randomized to receive eplerenone 25 to 50 mg/day (3,319 patients) or placebo (3,313 patients). Inclusion criteria were MI within 3 to 14 days; left ventricular ejection fraction of 40% or less or LVD by other tests plus CHF or DM; and optimal therapy including angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor inhibitors (ARBs), diuretics, beta-blockers (BB), or coronary reperfusion therapy. Exclusion criteria were use of potassium-sparing diuretics, serum creatinine greater than 2.5 mg/dL, and serum potassium greater than 5 mEq/L. Potassium levels were checked frequently and within 1 week of dose changes. Concurrent therapy with other agents known to be beneficial in treating CHF or MI was as follows: ACEI/ARB, 87%; BB, 75%; aspirin, 88%; and diuretics, 60%. The estimated benefits of eplerenone therapy at 1 year are given in the Table.

Despite exclusion of patients with renal dysfunction and high potassium levels at baseline, serious hyperkalemia (>6 mEq/L) occurred in 5.5% of the eplerenone group and 3.9% of the placebo group (P=.002). Hyperkalemia correlated with a lower creatinine clearance (Clcr). Serious hypokalemia (<3.5 mEq/L) occurred in 8.4% of the eplerenone group and 13.1% of the placebo group. No significant increase was noted in gynecomastia, breast pain, or impotence.

Hypertension

For mild-to-moderate hypertension, eplerenone produces significant decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) when compared with placebo, whether measured in the clinic or by ambulatory monitoring. Reduction is greater in SBP than DBP. Although the antihypertensive effect is dose dependent, most of the benefit is achieved with 100 mg/day. Eplerenone is 50% to 75% as effective as spironolactone, but has an effect equal to enalapril. As monotherapy for 12 months, eplerenone and enalapril controlled blood pressure (BP) in 55% and 53% of patients, respectively.

Eplerenone is effective regardless of renin levels; it is superior to losartan in black patients and as effective as losartan in white patients. In patients with systolic hypertension, eplerenone is equivalent to amlodipine in reducing SBP and pulse pressure, but not DBP. In patients with inadequate BP control with ACEI, ARBs, calcium-channel blockers, or BB monotherapy, addition of eplerenone lowers SBP in all groups but decreases DBP only in patients taking ARBs and BB. Eplerenone produces greater reductions in microalbuminuria than enalapril or amlodipine. It is as effective as enalapril in reversing left ventricular...
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Males and greater than 1.8 mg/dL in females, Clcr less than 50 mL/min, or concomitant use of potassium supplements or potassium-sparing diuretics.

References


Adverse events

In most studies adverse events were similar to placebo. Hyperkalemia is the most serious potential adverse event with eplerenone, although no significant increase was reported in most of the studies. However, patients with risk factors for hyperkalemia (renal disease/insufficiency, DM, mild hyperkalemia, or use of potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, and BB) were excluded from many of these studies, potassium levels were checked frequently, and patients in whom hyperkalemia developed were withdrawn. In hypertensive patients with DM and proteinuria, hyperkalemia was common, with potassium levels greater than 5.5 mEq/L seen in 33% of patients and 6.0 mEq/L or higher in 11% of patients. Gynecomastia or breast pain was reported in no more than 1% of patients. However, most studies were of short duration.

Contraindications

Eplerenone is contraindicated in patients with serum potassium greater than 5.5 mEq/L, Clcr of 30 mL/min or less, and concomitant use of strong CYP3A4 inhibitors. For hypertensive patients, eplerenone is contraindicated if they also have noninsulin-dependent DM with microalbuminuria, serum creatinine of greater than 2.0 mg/dL in males and greater than 1.8 mg/dL in females, Clcr less than 50 mL/min, or concomitant use of potassium supplements or potassium-sparing diuretics.

Table: Endpoints with eplerenone therapy compared with placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Eplerenone group (n= 3,319)</th>
<th>Placebo group (n= 3,313)</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
<th>Absolute risk reduction</th>
<th>Numbers needed to treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>14.4%</td>
<td>16.7%</td>
<td>0.85 (0.75–0.96)</td>
<td>0.008</td>
<td>2.3%</td>
<td>44 (25–174)</td>
</tr>
<tr>
<td>Death from CV causes or hospitalization from CV events</td>
<td>26.7%</td>
<td>30%</td>
<td>0.87 (0.79–0.95)</td>
<td>0.002</td>
<td>3.3%</td>
<td>31 (19–88)</td>
</tr>
<tr>
<td>Death from any cause or any hospitalization</td>
<td>52%</td>
<td>55%</td>
<td>0.92 (0.86–0.98)</td>
<td>0.02</td>
<td>3%</td>
<td>33 (19–147)</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>12.3%</td>
<td>14.6%</td>
<td>0.83 (0.72–0.94)</td>
<td>0.005</td>
<td>2.3%</td>
<td>44 (26–148)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, cardiovascular.
We found 4 randomized controlled trials addressing this question, 3 of them published in 2004. Three trials evaluated patients with history of gastroesophageal reflux disease (GERD) symptoms of at least 1-year duration. Of these, 2 studies found no benefit of *Helicobacter pylori* eradication and the third found higher rates of treatment failure with *H pylori* eradication. The fourth trial evaluated the impact of *H pylori* eradication on the development of new heartburn or reflux in a large population screened for *H pylori*.4

In the first trial patients with history of recurrent heartburn of at least 1-year duration with grade A esophagitis (patients with higher grades of esophagitis, peptic ulcer disease [PUD], or use of proton-pump inhibitors [PPIs] or H₂ receptor blockers within the previous month were excluded) or normal endoscopy were randomized to receive *H pylori* eradication treatment or placebo.2 Both groups were given omeprazole for 8 weeks. Patients were given antacids to use as rescue medication. Using life-table methods the probability of relapse defined as moderate-to-severe GERD symptoms was 83% at 12 months in both groups. No significant difference was noted in rates of esophagitis by follow-up endoscopy at 12 months in the 2 groups.

In the second trial 231 patients with GERD diagnosed either by endoscopy or 24-hour esophageal pH-metry, who had been on maintenance therapy with omeprazole for 12 months or longer, were randomized to *H pylori* eradication versus no eradication for 1 week and then continued on maintenance omeprazole therapy at previous doses.2 Patients with complicated PUD were excluded. After a 2-year follow-up the prevalence of reflux symptoms was similar in the eradication (25%) and noneradication groups (34%).

In the third trial 104 consecutive patients with weekly attacks of heartburn or acid regurgitation in the previous 12 months were enrolled.3 Patients with PUD, complications of reflux such as strictures or Barrett’s esophagus, and patients using non-steroidal anti-inflammatory drugs or PPIs within 4 weeks were excluded. Patients were randomized to either *H pylori* eradication treatment or omeprazole 20 mg bid with placebo antibiotics for 1 week followed by omeprazole 20 mg daily for 8 weeks. Patients with complete resolution of symptoms and esophagitis were maintained on omeprazole 10 mg daily for 52 weeks. A composite endpoint of treatment failure included incomplete resolution of symptoms or esophagitis at initial treatment (8-week period), or relapse of symptoms or esophagitis during maintenance phase. The 12-month probability of treatment failure was significantly higher in the eradication group (43.2%; 95% confidence interval [CI], 29.9%–56.5%) than in the placebo group (21.1%; 95% CI, 9.9%–32.3%). Most of this difference arose from initial treatment failure (5 of 53 in eradication group and 0 of 51 in the noneradication group), with relapse rates being similar (10 of 53 in eradication group and 8 of 51 in the placebo group). The placebo group also had lower reflux symptom scores (median score 0, range 0–1) than the eradication group (median score 1, range 0–2).

In a large community-based trial, 1,634 patients tested positive for *H pylori* (out of 10,537 screened).4 Of these, 1,558 were randomized to receive *H pylori*
eradication therapy or placebo. The principal outcome was the consultation rate for dyspepsia during a 2-year follow-up. Symptom frequency, symptom type, quality of life, and costs due to dyspepsia were secondary endpoints. *H pylori* eradication had no significant effect on the prevalence of heartburn (23.9% with treatment and 24.2% with placebo; odds ratio [OR] 0.99; 95% CI, 0.88–1.12) or reflux (18.9% with treatment and 17.6% with placebo; OR 1.04; 95% CI, 0.91–1.19). Treatment also had no impact on development of new heartburn (OR 0.90; 95% CI, 0.78–1.04) or reflux (OR 1.05; 95% CI, 0.90–1.21). In patients with these symptoms at baseline no significant improvement was seen for either heartburn (OR 0.90; 95% CI, 0.71–1.14) or reflux (OR 0.89; 95% CI, 0.62–1.29). Although the baseline characteristics of the total group of patients in the 2 arms were similar, the baseline characteristics of the subgroup of patients with reflux or heartburn were not given.

This relatively recent evidence indicates that *H pylori* eradication does not lead to improved outcomes in patients with GERD symptoms and does not prevent development of GERD symptoms in a screened population that tests positive for *H pylori*.

**REFERENCES**


