Interventions for heart failure

Evidence-based answer

The following interventions improve important outcomes in patients with systolic heart failure (all SORs: A, based on meta-analyses):

- Angiotensin converting enzyme (ACE) inhibitors reduce mortality, repeat myocardial infarction (MI), and hospitalization rates
- Beta-blockers and aldosterone blockers reduce mortality and hospitalization rates
- Diuretics reduce mortality and hospitalization rates and improve exercise capacity
- Digitalis treatment decreases hospitalization rates and clinical deterioration
- Aerobic exercise rehabilitation of at least 6 months in duration decreases hospitalization rates and improves quality of life

The following intervention improves important outcomes in African American patients with systolic heart failure (SOR: B, based on a single RCT):

- Isosorbide dinitrate and hydralazine combination therapy reduces mortality and hospitalization rates and improves quality of life

Evidence summary

A systematic review of 5 RCTs involving 12,763 patients (mean age 61 years) with left-ventricular dysfunction or clinical heart failure assessed the effect of ACE inhibitors versus placebo. About half (6,928) of these patients developed heart failure due to recent MI, whereas the other patients had no history of MI. Primary outcomes are given in the table for this study as well as other studies discussed below.

A systematic review of 22 RCTS involving 10,480 patients (mean age 61 years) with chronic heart failure examined the effects of beta-blockers versus placebo. Of the 22 trials, 2 used bisoprolol, 3 bucindolol, 8 carvedilol, 7 metoprolol, and 2 nebivolol in a double-blind randomized fashion and in a wide range of doses. Overall, the NNT with a beta-blocker to prevent 1 death was 20 and to prevent 1 hospitalization was 17.

A systematic review of 19 RCTs involving 10,807 patients with chronic heart failure or MI examined the efficacy of aldosterone blockade therapy. Spirolonlactone was the drug used most commonly, followed by eplerenone and canrenone. Risk reduction in hospitalizations was mostly seen in the
heart failure patients, while the post-MI patients had no significant change in hospitalization rate. A Cochrane review of 13 double-blinded RCTs involving 7,896 participants (mean age 58–69 years) with congestive heart failure examined treatment with digitalis versus placebo. Of the 13 RCTs, mortality was measured in 8 studies, hospitalization was measured in 4 studies, and clinical deterioration was measured in 12 studies. Clinical deterioration was described in the various studies as chest pain, breathlessness, tiredness, and difficulty walking.

A Cochrane review of 19 RCTs involving 3,647 participants (mean age 43–72 years) with chronic heart failure examined exercise rehabilitation versus a control group for treatment of heart failure. Most studies used the 21-question Minnesota Living with Heart Failure (MLWHF) questionnaire to measure QoL. The questionnaire measured changes in physical and social functions, such as walking, climbing stairs, being able to leave home, and recreational activities. Each answer on the questionnaire receives 0 to 5 points (0–105 total), and higher scores indicated a poorer QoL.

An RCT involving 1,050 African American patients with chronic heart failure examined the effect of isosorbide dinitrate/hydralazine combination therapy. Patients were randomly assigned a fixed dose of isosorbide dinitrate plus hydralazine or placebo, in addition to usual care. Mortality, hospitalizations, and HRQoL (MLWHF questionnaire) were measured. Mean duration of follow-up was 10 months. The study was terminated early (about 3 years later) due to a significantly higher mortality in the placebo group.

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**REFERENCES**


Perfect. Oh, by the way Osler, my patient in the hospital with the rash. The probabilities are 95% Henoch Schönlein purpura, 5% Wegener’s granulomatosis, and 2% Churg-Strauss syndrome. Okay, I’ll go with HSP. My next patient contracted pneumonia while at a Legionnaire’s conference. Osler, what empiric antibiotic should I use?

Me: This patient has an odd rash. What’s do you think it is, Osler? Osler: The probabilities are 95% Henoch Schönlein purpura, 5% Wegener’s granulomatosis, and 2% Churg-Strauss syndrome. Me: Okay, I’ll go with HSP. My next patient contracted pneumonia while at a Legionnaire’s conference. Osler, what empiric antibiotic should I use? Osler: You will get 88% coverage with azithromycin; 85% with levofloxacin; and 83% with tigecycline. Me: He’s pretty sick. What can I get with double coverage? Osler: 98.5% with azithromycin and levofloxacin. Me: Perfect. Oh, by the way Osler, my patient in the hospital with acute coronary syndrome will need a noninvasive cardiac study. Which one would be best? Osler: Retrieving demographic and comorbidity data for Mr. Reynolds. (Millisecond pause.) An adenosine MIBI has the optimum ROC curve.

It would be like having the smartest doctor in history looking over your shoulder and I can hardly wait. Sure, the original Watson generated some awesome TV ratings for 3 nights. But an Osler would generate some awesome clinical care every day. And with an Osler, the feeble-minded humans would always win.

Regards,

Jon O. Neher, MD

PS: I know Osler will read EBP, just like us. But faster.
**Postprostatectomy biofeedback**


This RCT studied use of behavioral therapy for incontinence persisting more than 1 year after radical prostatectomy. The study assigned 208 patients to 1 of 3 groups: behavioral therapy for 4 sessions over 8 weeks, behavioral therapy with biofeedback, and a control group that included an attention control.

Patients receiving behavioral therapy experienced significantly greater improvement in incontinence episodes at 8 weeks compared with the control group (55% reduction, a decrease from 28 to 13 episodes per week vs 24% reduction, a decrease from 25 to 20 episodes per week; *P* = .001 for percent reduction comparison). More patients in the behavioral therapy group were completely continent at 8 weeks (15.7% vs 5.9%, NNT=10). Patient adherence to behavioral therapy was high at 8 weeks (100%) and at 12 months (91%).

Improvement in treatment persisted at 12 months, but similar data for the control group were not reported. No differences in outcomes were noted between the group receiving behavioral therapy and the group receiving behavioral therapy with biofeedback.

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<tr>
<th>Relevant</th>
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<tr>
<td>Valid</td>
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<tr>
<td>Change in practice</td>
<td>Yes</td>
<td>Clinically meaningful</td>
<td>Yes</td>
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**Bottom line:** This appears to be the first study showing a benefit to late behavioral therapy for postprostatectomy incontinence, an intervention that is commonly used perioperatively and for nonsurgical incontinence. Although a benefit is apparent at 8 weeks, it is unclear if the improvement in urinary function at 1 year results from the intervention or natural resolution of the condition, because the control group was not queried at that time.

Family doctors seeing such patients should refer to physical therapy or behavioral therapy programs when available. Family physicians may also be able to obtain training to conduct these interventions themselves.

**Article Reviewer and Summary Author:** Umang Sharma, MD

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**A simple 2-step model for diagnosing obstructive sleep apnea**


This study involved the development and validation of a 2-step strategy for identifying moderate to severe obstructive sleep apnea (OSA). Patients at high-risk for OSA were identified and recruited through screening questionnaires in 6 primary care clinics in Australia. A small number of low-risk patients were also randomly selected to participate.

A total of 157 subjects completed 2 home sleep studies simultaneously: (1) ApneaLink monitoring (the test of interest) and (2) home polysomnography (the gold standard). The ApneaLink device has 2 channels that measure nasal airflow and oxygen saturation and generates an easily interpreted report automatically. By contrast, home polysomnography includes several measurements including nasal flow, oxygen saturation, chest excursions, and electroencephalogram and requires substantial expertise to interpret.

A 2-step diagnostic model consisted of completion of the 4-item “OSA50” questionnaire, which, if positive, was followed by home ApneaLink monitoring. The OSA50 questionnaire alone had a sensitivity of 100%, a specificity of 29%, and a negative predictive value (NPV) of 100% in the development group and an NPV of 95% in the validation group. The 2-stage model had a sensitivity of 88% (95% CI, 60%–98%), a specificity of 82% (70%–90%), a positive predictive value (PPV) of 56% (35%–75%), and an NPV of 96% (86%–99%) in the validation group.

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<tr>
<td>Change in practice</td>
<td>Yes</td>
<td>Clinically meaningful</td>
<td>No</td>
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**Bottom line:** The ApneaLink 2-step diagnostic strategy represents the first 2-step method to identify OSA in a primary care setting. The high NPV and low PPV make this model most useful for ruling out OSA. Unfortunately, the ApneaLink device does not provide recommended continuous positive airway pressure (CPAP) settings. Furthermore, Medicare will not cover CPAP treatment for OSA diagnosed in a home setting.

**Article Reviewer and Summary Author:** Kate Kirley, MD
Too many unknowns regarding CT screening for lung cancer


This RCT looked at efficacy of lung cancer screening by CT. Investigators assigned >50,000 current or former smokers with at least a 30-pack-year history of smoking to either yearly low-dose chest CT or chest radiography for 3 years; median follow-up was 6.5 years.

Lung-cancer-specific mortality was significantly lower in the CT group (346/26,455) than the radiography group (425/26,232, absolute risk reduction 0.32%, number needed to screen with CT to prevent 1 death from lung cancer per year=320). Overall mortality was also reduced in the CT group. Only 3.6% (649/18,146) of abnormal CT scans were confirmed lung cancer, and on further diagnostic testing after an abnormal CT, 28% of patients had complications.

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<td>Clinically meaningful</td>
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Bottom line: CT screening of patients at risk for lung cancer decreases mortality, but is associated with a high false-positive rate and subsequent morbidity. There was a persistently elevated rate of cancer detected in the CT group throughout the follow-up period, suggesting some of the cancers detected may not be clinically significant. The cost effectiveness of this screening intervention is also unknown.

Summary Authors: Nina V. Rogers, MD

Varenicline increases short-term CV risk


Postmarketing reports have indicated varenicline may increase the risk of cardiovascular (CV) events. This meta-analysis of 15 RCTs included published and unpublished data comparing varenicline with placebo in smokers. Patients in all studies except one were free of cardiovascular disease at the outset. Treatment period ranged from 7 to 52 weeks and follow-up from 24 to 52 weeks.

The study found an increase in CV events in patients receiving varenicline (Peto OR 1.72; 95% CI, 1.09–2.71). Overall mortality was not studied. Several sensitivity analyses were performed: excluding the most influential trial; including unverified CV events; including open-label trials; and including studies with an active comparator rather than placebo. These analyses had no significant effect on the results.

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<tr>
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<td>Yes</td>
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Bottom line: Results from this study suggest that varenicline increases short-term CV risk, but the study methodology was significantly flawed. The Peto method for pooling results was inappropriately applied. Furthermore, the summary risk of varenicline was applied to the baseline risk in a different population to calculate a misleadingly low number needed to harm. Varenicline may increase CV risk but this risk appears small, with a number needed to harm on the order of several hundred.

Summary Author: Umang Sharma, MD
Are adult patients with multiple skin lipomas at risk for other serious medical conditions?

Evidence-Based Answer
No evidence suggests that otherwise normal adult patients with multiple lipomas (>10) have increased health risks. However, several uncommon but serious syndromes are associated with multiple lipomas and some of these syndromes are associated with increased morbidity and mortality.

No data exist to suggest that having multiple lipomas (>10) are associated with increased health risks. However, several syndromes are associated with multiple lipomas, including Bannayan-Riley-Ruvalcaba syndrome, Gardner syndrome, Cowden syndrome, multiple endocrine neoplasia syndrome type I (MEN I), familial multiple lipomatosis, and multiple symmetric lipomatosis (MSL).

Some of these uncommon syndromes are associated with severe medical conditions. An example is MSL, a rare disorder with an incidence of about 1 in 25,000. This condition is characterized by massive fat accumulations around the neck, upper back, and shoulders. One prospective longitudinal study followed 31 patients with MSL over 4 to 26 years (mean, 15 years). Half of the patients developed paresthesias of upper and lower limbs, and about one-third experienced dyspnea, snoring, dysphasia, or sleep apnea. Many required surgical excision of the fatty growths. Almost three-quarters of the patients reported experiencing autonomic involvement including tachycardia, postural hypotension, and gustatory sweating.

Some of these syndromes associated with large numbers of lipomas can be mistaken for other severe disease conditions. For example, familial multiple lipomatosis has sometimes been mistaken for neurofibromatosis, which is sometimes associated with mental retardation.

What is the target heart rate in a patient with chronic atrial fibrillation?

Evidence-Based Answer
Strict heart rate control is not beneficial compared with more lenient heart rate control in well-compensated ambulatory patients with chronic atrial fibrillation. An acceptable target for resting heart rate is less than 110 beats per minute (bpm). (SOR: B, based on a single RCT and a practice guideline citing the same.)

An unblinded RCT evaluated lenient versus strict heart rate control in 614 patients with persistent atrial fibrillation. The investigators recruited physically active patients with baseline heart rates of more than 80 bpm at rest and without history of stroke or unstable heart failure. Patients were randomized to receive negative chronotropic medications to achieve a target resting heart rate of less than 110 bpm in the lenient rate control group and less than 80 bpm at rest and less than 110 bpm during moderate exercise in the strict rate control group. The primary outcome was a composite of cardiovascular death, congestive heart failure requiring hospitalization, stroke, systemic emboli, major bleeding, syncope, life-threatening adverse effects of rate-control drugs, sustained ventricular tachycardia, cardiac arrest, and implantation of a pacemaker or cardioverter-defibrillator.

Throughout the 3-year follow-up period, the mean resting heart rate achieved was 84 to 86 bpm in the lenient rate control group and 74 to 76 bpm in the strict rate control group. The 3-year estimated cumulative incidence of the primary outcome was 12.9% in the lenient rate control group and 14.9% in the strict rate control group, indicating lenient control was noninferior to strict control (absolute difference –2.0%; 90% CI, –7.6 to 3.5). Results may not generalize to patients with paroxysmal atrial fibrillation, unstable heart failure, history of stroke, as patients with these conditions were not studied.

A 2011 update of the American College of Cardiology/American Heart Association guideline on management of atrial fibrillation revised the recommendations on heart rate control based on the above study. The writing group recommended that strict heart rate control is not beneficial compared with lenient heart rate control (resting heart rate <110 bpm) in patients with persistent atrial fibrillation, stable left
ventricular function (ejection fraction >40%), and no or minimal symptoms. They qualified the recommendation by stating that uncontrolled tachycardia may over time be associated with a reversible decline in ventricular performance.

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Are topical heat wraps effective for acute low-back pain?

Evidence-Based Answer
Yes, topical heat wraps are effective treatment of acute and subacute low-back pain. (SOR: A, based on a systematic review and RCTs with consistent findings.)

A Cochrane review of 9 RCTs and nonrandomized controlled clinical trials examined superficial heat or cold therapies for low-back pain, compared with placebo, no therapy, or other therapies.1 Participants were 18 years or older with nonspecific low-back pain. The primary outcomes measured were pain and physical functional status.

In 2 of the trials, in which 258 patients had a mix of acute (<6 weeks) and subacute (6–12 weeks) low-back pain, heat wrap therapy significantly reduced pain after 5 days (weighted mean difference (WMD) 1.06; 95% CI, 0.68–1.45; scale range, 0–5) compared with oral placebo. One trial of 90 participants with acute low-back pain found that a heated blanket compared with a nonheated blanket significantly decreased acute low-back pain 25 minutes after application (WMD −32.20; 95% CI, −38.69 to −25.71; scale range, 0–100).2

The trials included were of varying methodological quality, with 5 of the 9 trials being rated as high quality (based on a risk of bias assessment) and 4 as low quality. Evidence was insufficient to evaluate the effects of cold for acute low-back pain.1

In a 2006 RCT of 32 healthy adults without back pain (asymptomatic), heat wrap therapy (n=16) was compared with cold pack therapy (n=16) after patients performed an exercise protocol designed to induce delayed-onset muscle soreness of the low back.3 At 18 hours postexercise, participants applied either a heat wrap or a cold pack. The heat wrap was applied 2 times for 8 hours each beginning at hours 18 and 32 postexercise. The cold pack was applied for 15 to 20 minutes every 4 hours between 18 and 42 hours postexercise.

Using a 6-point pain relief score, at 24 hours postexercise the mean pain relief score for the heat wrap group was significantly greater than for the cold pack group (1.5 vs 0.6, respectively; P=.026). This study was supported by Procter & Gamble, a manufacturer of heat wraps.2

A 2005 RCT compared heat wrap therapy plus education with education only in 43 adult patients (ages 20–62) who presented to an occupational injury clinic with an acute episode of low-back pain.3 Eighteen patients were assigned to the education-only group (written handout on recognition and treatment of low-back pain) and 25 patients were assigned to the ThermaCare Heat Wrap group (applied daily for 3 consecutive days, removed at the end of the day) combined with the educational handout. Pain intensity was measured on a 0 to 10 categorical scale and pain relief was measured on a 0 to 5 scale (0=no relief, 5=complete relief). Patients completed both scales 4 times daily for 14 days.

Compared with the education-only group, the heat wrap group had significantly lower pain intensity during the 3-day treatment period (weighted mean difference [WMD] −2.05 on day 3; 95% CI, −3.34 to −0.76). Better scores persisted to the last day of follow-up (WMD −1.63 on day 14; 95% CI, −2.92 to −0.34). Pain relief was also significantly better in the heat wrap group during therapy (WMD 1.53 at day 3; 95% CI, 0.76 to 2.3) and persisted through the end of the study (WMD 1.21 on day 14; 95% CI, 0.26 to 2.14).3

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Do NSAIDs delay bone healing in patients with acute fractures?

Evidence-Based Answer
There appears to be an association between nonsteroidal anti-inflammatory drug (NSAID) use and delayed bone healing in the setting of acute fractures. (SOR: B, based on inconsistent RCTs and retrospective cohort trials.)

A prospective double-blinded RCT of 42 postmenopausal women with a displaced Colles’ fracture compared the effects of piroxicam on fracture healing and bone density. Twenty-one patients were prescribed piroxicam 20 mg/d for 8 weeks and the control group (21 patients) received a matching placebo. At 8 weeks the bone mineral content (by single photon absorptiometry) of the fractured forearm was measured as a percentage value of the contralateral arm.1

Patients receiving piroxicam had less decrease in bone density of the radius and ulna (7% and 5%) compared with matched placebo controls (10% and 7%). No differences in recovery were identified between the groups. The authors concluded that piroxicam did not decrease the rate of fracture healing.1

In a prospective randomized trial (n=112), patients underwent an open reduction and internal fixation of an acetabular fracture with concomitant long bone fracture. Indomethacin was studied to determine if it would prevent heterotopic ossification, which is a common complication of acetabular fractures. The patients were randomized into 3 arms: 36 received no prophylaxis, 38 received focal radiation, and 38 received 6 weeks of indomethacin (25 mg 3 times daily). Twenty-nine percent of patients receiving indomethacin (11 of 38) had nonunion versus 7% (5 of 74) of those not receiving indomethacin (P=.004).2

Additional studies show conflicting data (TABLE). There currently are no specific guidelines by the American Academy of Orthopedic Surgeons or the American College of Sports Medicine on the use of NSAIDs for analgesia in the setting of acute fractures.

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department or the US Army at large.


<table>
<thead>
<tr>
<th>Study</th>
<th>N, type of fracture</th>
<th>Medication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>9,995 patients with humeral shaft fractures</td>
<td>NSAIDs vs control</td>
<td>Increased risk of nonunion with NSAID use days 1–90 postfracture RR=3.7 (95% CI, 2.4–5.6)</td>
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<tr>
<td>Retrospective</td>
<td>288 patients with spinal surgery</td>
<td>Ketorolac vs control</td>
<td>Increased risk of nonunion 17% vs 4%; OR 4.9 (95% CI, 1.8–16.6; P&lt;.001)</td>
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<tr>
<td>Retrospective</td>
<td>99 patients with femoral diaphysis fracture</td>
<td>Diclofenac and ibuprofen vs control</td>
<td>Increased risk of nonunion OR 11 (95% CI, 3.5–33; P=.0001)</td>
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<tr>
<td>Retrospective</td>
<td>94 patients with tibial fractures</td>
<td>NSAIDs vs control</td>
<td>Increased length of time to union 17 vs 24 weeks (P=.0003)</td>
</tr>
</tbody>
</table>

CI=confidence interval; control=no NSAID use; NSAIDs=nonsteroidal anti-inflammatory drugs; OR=odds ratio; RR=relative risk.

TABLE
Studies concerning NSAIDs in bone healing

What is the safest antidepressant medication for use in pregnancy?

**Evidence-Based Answer**

In treating pregnant patients with depression, no single agent stands out as offering a clear safety advantage over another. The most consistently noted morbidity with maternal antidepressant use is preterm birth. Paroxetine may increase the risk of congenital cardiac malformations, but the data are inconsistent. (SOB: B, based on systematic review of cohort and case-control studies.) In general, antidepressant selection should be made based on patient and family history of a favorable response. (SOR: C, based on expert opinion.)

A systematic review examined potential risks associated with antidepressant exposure during pregnancy. It included 6 meta-analyses (n=40,340), 26 prospective cohort studies (n=123,992), 14 retrospective cohort studies (n=2,836,600), and 11 case-control studies (n=140,253) evaluating risks associated with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, monoamine oxidase inhibitors (MAOIs), tetracyclines, and trazodone. Of the various endpoints evaluated, neonatal adaptation syndrome, preterm birth, and congenital malformations were shown to have the strongest correlation between drug exposure and incidence.

Neonatal adaptation syndrome related to antidepressant exposure was reported in 15 (n=7,869) of the 17 (n=7,900) studies that addressed neonatal adaptation, but markers of this endpoint varied from irritability to neonatal intensive care admission. This outcome was seen in cohorts using SSRIs and venlafaxine. No difference was apparent in the incidence of neonatal adaptation syndrome between venlafaxine and SSRIs.

Preterm birth was associated with antidepressant (SSRIs, TCAs, tetracyclines, MAOIs, SNRIs, mirtazapine, and bupropion) exposure in 15 of 19 studies reporting this outcome. Increased risk was not associated with any particular agents or class, but remained relatively consistent across all classes of antidepressants. Many studies in this analysis did not account for confounding preterm birth risks such as severity of underlying depression, maternal age and weight, and smoking.

Links between congenital malformation and first trimester antidepressant exposure have been conflicting. The authors of this systematic review concluded that paroxetine may be associated with cardiac malformations, but conceded that the results of case-controlled, retrospective, and prospective cohort studies and birth registries investigating this correlation have been inconsistent.¹

A prospective cohort study of women exposed to various SSRIs, SNRIs, bupropion, mirtazapine, and trazodone during their first trimester (n=928) investigated the risk of 24 major malformations associated with antidepressant exposure.² Rates of major malformations did not differ between groups exposed to antidepressants and those not exposed (2.5% and 2.6%, respectively; RR=0.96; 95% CI, 0.55–1.67). No particular malformation pattern was noticed in either group. Malformation rate and type was indiscriminate of specific antidepressant agent, including paroxetine (n=148).

The American Psychiatric Association guidelines state the overall risk of teratogenicity with antidepressants appears low, and recommend that choice of antidepressant be based on past history of favorable response and available safety data of the specific agent.³ The guidelines recommend avoiding paroxetine during the first trimester due to risks of cardiac malformations. Monotherapy is preferred and switching medications during pregnancy is not recommended.

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What are the appropriate clinical endpoints for managing acute fluid overload in a patient with diastolic heart failure?

Evidence-Based Answer
Therapeutic endpoints for managing acute fluid overload in patients with diastolic failure are the same as those used in managing acute systolic heart failure: resolution of rales and dyspnea, reduction of weight, improvement of peripheral edema, and normalization of jugular venous distension (JVD). Blood pressure and heart rate should be controlled. (SOR: C, based on consensus guidelines.)

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) collaborate on cardiac guidelines using consensus expert opinion after a review of the scientific literature. Scientific literature is rated according to ratings given in the TABLE.

The ACCF/AHA guidelines on heart failure in adults were published in 2005 and updated in 2009.1

### TABLE

<table>
<thead>
<tr>
<th>ACCF/AHA classification of recommendations and level of evidence1</th>
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<tbody>
<tr>
<td>Rating</td>
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</tr>
<tr>
<td>Class I</td>
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<td>IIa</td>
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<td>IIb</td>
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<th>Level of evidence</th>
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<tr>
<td>A</td>
<td>Data derived from multiple clinical trials or meta-analyses</td>
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<tr>
<td>B</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td>C</td>
<td>Consensus opinion of experts, case studies, or standard of care</td>
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ACCF=American College of Cardiology Foundation; AHA=American Heart Association.


Does an aerobic exercise regimen affect glycemic control in patients with type 2 diabetes?

Evidence-Based Answer
Yes. Improvements are clearly seen with 1 hour of moderate intensity exercise 3 to 4 times a week. (SOR: A, based on a meta-analysis.) Increasing energy expenditure as little as 10 metabolic equivalents (METS) per hour per week likely has some benefit. (SOR: B, based on a single RCT.)

A meta-analysis of 14 controlled trials (n=504) with 11 RCTs reviewed and quantified the effects of physical activity on glycosylated hemoglobin (HbA1c) and body mass in patients with type 2 diabetes.1 Participants were adults (mean age, 55 years), half of whom were female, who had type 2 diabetes for 4.3±4.6 years, with therapy duration longer than 8 weeks. Pharmacotherapy was allowed but not required for inclusion. There were 2 resistance training studies and 12 aerobic activity studies with...
3 to 4 moderate-intensity 1-hour exercise sessions per week for an average of 18 weeks.

Meta-analysis of the 12 aerobic training studies demonstrated that HbA1c values between the control and postinterventional groups decreased by 0.66% ($P<.001$), with insignificant HbA1c differences in subgroup analysis between aerobic and resistance exercise groups.¹

One RCT (n=179) determined the long-term impact of physical activity of various intensity on HbA1c in patients with type 2 diabetes (mean age, 62 years).² Subjects were randomly assigned to 1 of 6 interventions of differing METS per hour per week. (Results shown in the **TABLE**).

An observational study with 142 adults (mean age, 72 years) with a mean body mass index of 29 kg/m² investigated the relationship between exercise duration and HbA1c in a multiethnic geriatric population. Oral hypoglycemic medications were allowed but were not an inclusion criterion.³ Data included anthropometric measurements, HbA1c, and pedometer readings. On average, the subjects reported taking 3,939±232 steps (approximately 2.0 miles) daily.

Subjects with HbA1c levels lower than 7.0% and fasting serum glucose lower than 100 mg/dL walked approximately 1,343 steps (0.5–0.75 miles) daily more than those with abnormal HbA1c or fasting plasma glucose levels.³

### Table: Effect on HbA1c of increasing exercise intensity in patients with diabetes after 2 years²

<table>
<thead>
<tr>
<th>METS increase (per hour per week)</th>
<th>Group size (n)</th>
<th>HbA1c change (mg/dL)</th>
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<tbody>
<tr>
<td>0.6±0.3</td>
<td>28</td>
<td>+0.03</td>
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<tr>
<td>6.3±0.4</td>
<td>27</td>
<td>–0.06</td>
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<tr>
<td>17.1±0.4</td>
<td>31</td>
<td>–0.4</td>
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<td>27.0±0.5</td>
<td>27</td>
<td>–0.9</td>
</tr>
<tr>
<td>37.5±0.5</td>
<td>32</td>
<td>–1.1</td>
</tr>
<tr>
<td>58.3±1.8</td>
<td>34</td>
<td>–1.0</td>
</tr>
</tbody>
</table>

Physical exercise with energy expenditure >10 METs per hour per week (ie, jogging at 6 mph for 1 h/wk or brisk walking at 4 mph for 2 h/wk) significantly affected HbA1c in adults with type 2 diabetes. HbA1c=glycosylated hemoglobin; METS=metabolic equivalents.

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**Special Thanks**

The HelpDesk Answers project would like to recognize several faculty members who have contributed significantly by volunteering to peer review extra manuscripts.

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Intramuscular vs intravenous oxytocin for active management of the third stage of labor

**Bottom line**
There are no RCTs or other quality evidence to recommend either intramuscular (IM) or intravenous (IV) oxytocin over the other for management of the third stage of labor. Professional bodies recommend both routes of administration equally.

**Background**
A 2010 Cochrane review found that active management of the third stage of labor with oxytocin and gentle cord traction after delivery of the anterior shoulder (vs expectant management) reduced both postpartum hemorrhage (PPH) of >1,000 mL (RR=0.34; 95% CI, 0.14–0.87; 3 trials, 4,636 women) and maternal hemoglobin <9 g/dL after birth (RR=0.50; 95% CI, 0.30–0.83; 2 trials, 1,572 women).

A 2010 Cochrane review of 7 studies involving more than 3,000 women showed that active management of the third stage of labor using oxytocin rather than no uterotonic agents resulted in fewer deliveries with blood loss of >500 mL (RR=0.50; 95% CI, 0.43–0.59) and less need for therapeutic oxytocic agents (RR=0.50; 95% CI, 0.39–0.64).

A 2007 Cochrane review found that, compared with oxytocin, misoprostol for the active management of the third stage of labor resulted in higher risk of severe PPH (RR=1.32; 95% CI, 1.2–1.5; 16 trials, 29,042 women). The use of additional uterotonic agents apparently increased when misoprostol was used instead of oxytocin, but results were not totaled because of statistical heterogeneity. Use of oxytocin compared with misoprostol showed a trend toward fewer blood transfusions (RR=0.81; 95% CI, 0.64–1.02; 15 trials, 27,858 women). Misoprostol also resulted in more side effects than oxytocin.

While evidence supports oxytocin for active management of the third stage of labor, providers may have questions about the best route (IV or IM).

**Evidence summary**
The onset of action of IV oxytocin is less than 1 minute compared with 3 to 5 minutes for IM oxytocin. The length of contractions caused by IV oxytocin depends on the length of infusion, but may continue for an hour after stopping the medicine. A single dose of IM oxytocin may cause contractions for 2 to 3 hours.

No studies could be identified comparing outcomes for IV versus IM oxytocin for prevention of PPH. Professional bodies including the American College of Obstetrics and Gynecology, the American Academy of Family Physicians, and the Society of Obstetricians and Gynecologists of Canada recommend IV and IM oxytocin equally for active management of the third stage of labor.

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**REFERENCES**

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**Evidence You Can Trust**
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You have our word on it.
Herpes zoster

Painful vesicular rash, also known as shingles, caused by reactivation of the varicella-zoster virus (VZV) within the dorsal root or cranial nerve ganglia.

Incidence, prevalence
- One million cases each year in the United States
- Most cases affects persons between the ages of 50 and 79 years

Morbidity, mortality
- Postherpetic neuralgia (PHN)
  - No standard definition because the pain may last 30 days to more than 6 months after the lesions have healed
  - Occurs in 15% of cases
- Herpes zoster ophthalmicus (ocular zoster)
  - Occurs in 5% to 10% of cases
  - Need urgent ophthalmology referral
  - May lead to permanent vision loss and cranial nerve palsies
- Superimposed bacterial infections
- Rare disseminated cutaneous and visceral disease can be seen in severely immunocompromised patients (meningoencephalitis, myelitis)

Recommendations
- Antiviral medication should be started within 72 hours of symptom onset in acute herpes zoster to increase healing and decrease pain caused by the acute rash (SOR: A)
- Tricyclic antidepressants, opioids, gabapentin, or pregabalin may be used to decrease the pain of PHN (SOR: A)
- Capsaicin or a lidocaine patch may be used to decrease the pain of PHN (SOR: B)

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Pyelonephritis

Pathology
- Escherichia coli most common pathogen in uncomplicated cases (70%–80%)
- Klebsiella spp 6% to 10% (increased rate among patients aged >55 years)
- Enterococcus spp 3% to 7%
- Staphylococcus saprophyticus: <3%

Microbiology
- May be significantly different in complicated pyelonephritis: E coli still most common
- Includes Citrobacter, Enterobacter, Pseudomonas aeruginosa, enterococci, Staphylococcus aureus, and fungi

Incidence, prevalence
- Estimated 250,000 hospitalizations annually
- Affects more women than men
- Higher mortality rates in males vs females in complicated pyelonephritis

Therapeutics
- Start empirical antibiotics then change agents based on culture results
- Duration of therapy
  - Not influenced by presence of bacteremia
  - 14-day regimen of antibiotics recommended (SOR: A)
  - 7–10 days mild illness and patients who have rapid response to therapy (SOR: B)
  - 7-day course ciprofloxacin more favorable outcome than 14-day course of trimethoprim-sulfamethoxazole
  - Levofloxacin FDA approved 5-day course of 750 mg PO daily for treating uncomplicated pyelonephritis only
  - Beta-lactam regimens <14 days have high failure rates
    - 21-day treatment for slow response to therapy or severe illness

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What impact does hCG therapy have on patients with obesity?

Bottom line

Human chorionic gonadotropin (hCG) does not cause weight loss, reduce hunger, redistribute fat from the abdomen and hips, or create a feeling of well-being without weakness. (SOR: A, based on a meta-analysis.)

Evidence summary

A meta-analysis identified 14 RCTs (N=605) that assessed if hCG therapy played a role in weight loss. All included calorie restriction in the placebo groups. Methodological quality was highly variable.

Weight loss likely the effect of severely restricted calorie intake

Of the 14 randomized studies, 2 studies had positive outcomes whereas 12 studies showed no effect from using hCG. Only 5 of the RCTs reported on all 4 major outcomes (weight loss, fat redistribution, hunger, feeling of well-being). The authors concluded that any weight loss was likely the result of severely restricted caloric intake and that hCG has no effect on hunger reduction, redistribution of fat, or feeling of well-being. The 2 RCTs of highest design quality are described below.

No effect on weight loss or body fat loss

One was a double-blind, controlled crossover study of 202 patients comparing hCG injections and caloric restriction (with a 500 calorie per day diet) with placebo and caloric restriction. This study consisted of a 6-week treatment phase with 125 units of hCG injections or placebo for 6 days of each week, followed by a 6-week maintenance phase of no therapy. During the maintenance phase, the patients were given instructions on a gradual increase in calories, with the goal of keeping the weight stable. Then they underwent another 6 weeks of injections: those who received hCG the first time received placebo and vice versa. This treatment phase was followed by another 6-week maintenance phase.

The overall mean weight loss in subjects receiving hCG injections was no different from that in the placebo group (−6.8 vs −7.0 kg, respectively; P>.1). Likewise, body fat loss was similar with hCG and placebo (−3.2% vs −3.4%, respectively; P>.1).

No effect on hip/waist circumference, hunger response, or weight loss

The other higher quality trial studied 51 women between the ages of 18 and 60 years and compared 125 units hCG plus a 500 calorie per day diet with placebo plus a 500 calorie per day diet over 32 days. All patients were weighed daily and reported their degree of hunger on a 5-point scale from absence of appetite to severe hunger. Also, all patients had their hip and waist circumference measured on a weekly basis.

The mean percentage changes in hip and waist circumferences were not significantly different between the 2 groups. Also, no statistically significant difference was found in the hunger responses between the 2 groups. The mean total weight loss was 15.8 lb in the hCG group and 15.5 lb in the placebo group (P>.1).

REFERENCES

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For each question, please mark the single best answer by checking the appropriate box.
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1. Which of the following outcomes is most likely to be associated with use of antidepressant medication during pregnancy?
   - a. Persistent pulmonary hypertension
   - b. Preterm birth
   - c. Spontaneous abortion
   - d. Abnormal birth weight

2. For back pain, heat wraps:
   - a. Are effective for acute injuries but not subacute pain
   - b. Are not as effective as cold packs
   - c. Produce effects that last beyond the duration of therapy
   - d. Are not effective if used the same day as stressful exercise

3. According to guidelines from the American College of Cardiology Foundation/American Heart Association, with patients being treated for acute diastolic heart failure, what components should be monitored?
   - a. Weight, peripheral edema, pulmonary congestion, vital signs, jugular venous distension (JVD)
   - b. Abdominal girth, weight, vital signs
   - c. B-type natriuretic peptide, weight, vital signs, JVD
   - d. Echocardiography, weight, vital signs, JVD

4. For patients with type 2 diabetes:
   - a. Aerobic exercise must occur daily to have an impact on hemoglobin A1c values
   - b. Resistance exercise is associated with increased hemoglobin A1c values
   - c. Resistance exercise is clearly less effective than aerobic exercise in altering hemoglobin A1c values
   - d. Both aerobic and resistance are associated with lower hemoglobin A1c levels

5. Which statement below is true regarding nonsteroidal anti-inflammatory drug (NSAID) use and bone healing?
   - a. NSAIDs are recommended for analgesia in all acute fractures
   - b. NSAIDs consistently show improved bone healing in humans
   - c. The American College of Sports Medicine recommends the use of NSAIDs in acute fractures
   - d. There appears to be an association between delayed bone healing and NSAID use in acute fractures

6. Which of the following statements is true regarding intravenous (IV) oxytocin?
   - a. It has a slower onset of action than intramuscular (IM) oxytocin
   - b. High-quality RCTs have demonstrated efficacy equivalent to IM oxytocin in active management of the third stage of labor
   - c. Professional bodies recommend it over IM oxytocin for active management of the third stage of labor
   - d. No studies demonstrate worse or better outcomes compared with IM oxytocin for active management of the third stage of labor

7. What is the recommended target heart rate for a patient with chronic atrial fibrillation?
   - a. Heart rate >150 beats per minute with moderate exercise
   - b. Resting heart rate <80 beats per minute
   - c. Resting heart rate <110 beats per minute
   - d. Resting heart rate of 70–90 beats per minute

8. Which of the following syndromes is associated with multiple lipomas?
   - a. Multiple endocrine neoplasia syndrome type I
   - b. Dubin-Johnson syndrome
   - c. McArdle syndrome
   - d. Peutz-Jeghers syndrome
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