POEMs

Patient-Oriented Evidence that Matters

Each month, the POEMs editorial team reviews more than 90 journals of interest to primary care physicians, identifying the articles you have to know about to stay up to date. We call these articles POEMs (Patient-Oriented Evidence that Matters) because they deal with common primary care problems, report outcomes that matter to patients, and have the potential to change the way we practice. The eight most important articles are critically appraised each month by a team of more than 50 reviewers who make a recommendation for clinical practice. The collected reviews of the POEMs are available at the Journal's World Wide Web site at http://jfp.msu.edu

Radiologic Evaluation of Crohn's Disease

Bernstein CN, Boult IF, Greenberg HM, et al. A prospective randomized comparison between small bowel enteroclysis and small bowel follow-through in Crohn's disease. Gastroenterology 1997; 113:390-8.

Clinical question **Is enteroclysis or small bowel follow-through more accurate, better tolerated, and safer among patients with known Crohn's disease who require radiological assessment for staging or determination of recurrence?**

Background Crohn's disease is a common, chronic inflammatory disease that can affect the gastrointestinal tract anywhere from the mouth to the anus. More than 50% of patients with Crohn's disease have involvement of the distal ileum, and 25% have exclusive involvement of this area. Since no endoscopic technique has been developed to directly visualize the mid- and distal-small bowel, physicians must rely on radiographic techniques. Previous retrospective studies comparing these two techniques have favored enteroclysis as the procedure of choice.[1-3]

Population studied Consecutive patients with known Crohn's disease from the practices of three participating gastroenterologists were invited to participate. All required radiological assessment of their small bowel for either staging of extent of disease or determination of recurrence of disease. Of the 27 patients included in the study, 7 were men. The group had a mean age of 36 years, and a mean disease duration of 8.8 years.

Study design and validity This was a prospective randomized, crossover trial comparing the accuracy, time involved, radiation dose, and tolerance for small bowel enteroclysis (SBE) compared with small bowel follow-through (SBFT) in patients with known Crohn's disease. Patients were blindly randomized into four possible combinations of study sequences based on radiologist and study type. Once randomized, the patients initially underwent an SBE or SBFT performed by one of two participating radiologists. The patient returned within 2 weeks for the alternative procedure by the second radiologist, who was blinded to the results of the first study. An adaptation of a previously validated scoring sheet was used for each radiologic study, with the radiologists blinded to the score given by the first radiologist. An independent investigator reviewed the scoring. Within two weeks of completing both studies, patients were contacted and asked their preferences between the two preferences. Of the 27 patients enrolled, one was excluded for improper enrollment. The remaining 26 patients completed all aspects of the study. While the total number of patients is small, the crossover design, with each patient serving as their own control, assured adequate sample size.

Outcomes measured The primary outcome was the ability to detect the presence of small bowel abnormalities. Secondary outcomes included the radiation dose, technical difficulty, and patient preference for the procedure.

Results Sixteen patients underwent SBFT as the initial study, with a mean time between procedures of 8.7 days. The SBE and SBFT were both diagnostic of Crohn's disease in 15 cases. The SBFT more accurately reported mucosal detail (n=3) and a greater number of fistulas (n=2); the SBE more accurately reported how much of the bowel was involved (n=1). In a total of 4 cases, SBE missed duodenal disease. Intraclass correlation between radiologist for the presence of small bowel disease was much higher for SBFT than for SBE. The mean radiation dose was much higher and the fluoroscopy time was much greater for SBE than for SBFT. When questioned, 26 of 27 patients preferred SBFT to SBE.

Recommendations for clinical practice **This is the only randomized, blinded, prospective crossover study to directly compare SBE and SBFT for the detection of Crohn's disease in the small bowel. The results of this study show that SBFT offers comparable accuracy to SBE in detection of small bowel Crohn's disease. It has the added advantages of a lower radiation dose, reduced radiologist time for the study, and it is overwhelmingly preferred by patients. Whether SBFT is the better study for initial diagnosis of Crohn's disease is still unanswered. For patients with known Crohn's disease, however, SBFT is bet-**

ter than SBE to ascertain extent of small bowel disease and to determine recurrences of disease.

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D-Dimer Testing for PE

Perrier A, Desmarais S, Goehring C, et al. D-dimer testing for suspected pulmonary embolism in outpatients. Am J Respir Crit Care Med 1997; 156:492-96.

Clinical question **Can D-dimer results exclude pulmonary embolism?**

Background Pulmonary embolism (PE) is life-threatening and somewhat common in primary care, but controversy remains about the appropriate diagnostic strategy. The PIOPED study established that clinical estimates of probability and ventilation/perfusion (V/Q) scans eliminate the need for pulmonary angiograms in approximately 15% to 30% of patients with symptoms. D-dimers and lower extremity ultrasounds have been advocated to further reduce the need for pulmonary angiography; this report examines the diagnostic value of D-dimers, especially for their ability to rule out PE.

Population studied The study population was 742 adults presenting consecutively to a university emergency department (ED) with symptoms suggestive of PE. Patients with prior deep venous thromboses (DVTs), who had received prior V/Q scans, or with suspected PE in the course of hospitalization elsewhere were excluded. The source of referral to the ED and the specific symptoms used to include patients were not described, but it is likely that this population is similar to that which family physicians would transfer from their office for evaluation of possible PE.

Study design and validity This report comes from a case series evaluating the effectiveness of a diagnostic strategy thath combines residents' formal clinical estimates of PE probability, a V/Q scan, D-dimer measurement, and lower extremity ultrasound; pulmonary angiography is reserved for those patients in whom uncertainty remained.[1] A strength of the study is the size of the case series, but a more detailed description of how symptoms and signs were converted to clinical estimates would have been valuable.

The criteria for diagnosis of PE included a high probability lung scan, DVT by ultrasound and nondiagnostic lung scan, high clinical probability and nondiagnostic lung scan, or pulmonary angiogram with embolus; PE was excluded in patients with a D-dimer of <500 µg/L, a normal lung scan, a normal angiogram, or the combination of low clinical probability and nondiagnostic lung scan. Patients who were believed not to have PE were followed up for 3 months for evidence of recurrent thromboembolism. Assessing the performance of D-dimer independently is difficult with this study design, since the gold standard test, pulmonary angiography, was done on only 21% of the patients, and the clinical diagnostic decision substituted for angiography depended on D-dimer results in 29% of the cases. It is not appropriate to compare a test against a standard that incorporates the test result.

The authors also compared negative D-dimers with clinical follow-up for evidence of thromboembolism. How good a system is this? The classic article demonstrating the effectiveness of anticoagulation describes a rate of more than 50% death and major recurrence for PE in 10 to 28 days;[2] it is thus likely that using a 3-month follow-up will capture the most clinically significant recurrences, but will miss some pulmonary emboli.

Outcomes measured The primary outcomes were the sensitivity, specificity, and negative predictive value of D-dimers for the diagnosis of PE.

Results The prevalence of PE was 29%, and follow-up of patients classified as without PE was 98.7%. Of 198 patients with D-dimer <500 µg/L, only one, who was lost to follow-up, might have had a false-negative D-dimer result. The sensitivity was 99.5% (95% CI, 97.2 to 100.0), specificity 41.4% (95% CI, 37.0 to 45.9) and negative predictive value of 99.5% (95% CI, 97.2 to 100.0). We calculated positive and negative likelihood ratios of 1.7 and 0.01.

Recommendations for clinical practice **This study provides good evidence that patients with an ELISA D-dimer concentration of < 500 µg/L have a very low risk of thromboembolism over 3 months. Combining this report with other recent evaluations of D-dimers, it seems reasonable to incorporate this test into a diagnostic strategy for pulmonary emboli, particularly when combined with a low clinical estimate of probability or low-probability lung scans, to exclude PE and obviate angiography. There are, however, several important practical caveats: (1) the D-dimer test is very nonspecific, and elevated D-dimers do not definitely indicate PE, (2) the results do not necessarily apply to postoperative patients or patients with DVT, and (3) the ELISA tests used for this study**

are slow and not routinely available yet. The results cannot be generalized yet to the less expensive, faster latex agglutination kits, which would be more feasible to employ in real time in the emergency setting.

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Low-Molecular-Weight Heparin for PE

Simonneau G, Sors H, Charbonnier B, Page Y, Laaban J, Azarian E, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997; 337: 663-9.

Clinical Question **Is tinzaparin (a low-molecular-weight heparin) therapy equivalent to standard, unfractionated heparin in the treatment of acute pulmonary embolism?**

Background Low-molecular-weight heparins (LMWHs) have been well studied in the treatment of deep venous thrombosis (DVT), with at least 25 different prospective trials and three meta-analyses showing them to be safe and effective alternatives to standard unfractionated heparin for treating DVT. Conversely, there have been few studies of LMWHs for the treatment of pulmonary embolism, and they have been limited by small sample sizes, short follow-ups, and use of intermediate, disease-oriented outcomes such as angiographic changes.

Population Studied Consecutive patients older than 18 years of age presenting to 57 centers in Europe were included. Pulmonary embolism was confirmed by angiography, high-probability ventilation/perfusion scan, or intermediate-probability scan in the setting of documented DVT. No information is provided about the practice setting (primary or referral) of participating centers.

Study design and validity This was a prospective, randomized, nonblinded trial comparing treatment with once-daily weight-based subcutaneous dosing of tinzaparin with control treatment with standard continuous adjusted-dose intravenous unfractionated heparin. Inclusion and exclusion criteria were clearly stated, and baseline characteristics of the study and control patients were similar. The patients received heparin therapy for a minimum of 5 days. Oral anticoagulants were begun between the first and third days of treatment, and continued through the 3 months of follow-up. Data were appropriately analyzed on an "intention-to-treat" basis.

A potential source of bias in this study was the inability to blind the treating physicians, who made clinical judgments regarding the endpoint of symptomatic recurrent thromboembolism. This was minimized, however, because all participants underwent repeat scintigraphic scanning on the eighth day, and the readers of all radiologic studies were blinded. Another potential source of bias is the large percentage of patients (73%) in the LMWH group who received therapeutic doses of unfractionated heparin for an average of 18 hours prior to randomization.

Outcomes measured The primary endpoint was a combination of death, recurrent thromboembolism, or major bleeding (resulting in a 2 g drop in hemoglobin, requiring transfusion of two or more units, or any intracranial or retroperitoneal bleeding). A secondary endpoint measured changes in scintigraphically detectable pulmonary vascular obstruction.

Results A total of 612 patients were randomized, 308 to unfractionated heparin and 304 to LMWH. In the first 8 days of the study, the primary endpoint was reached by 3% of patients receiving LMWH, and 2.9% of controls receiving unfractionated heparin. At 90 days, the primary endpoint was reached by 5.9% of those who received LMWH, and 7.1% of controls (absolute risk difference 1.2%; 95% CI, 2.7 to 5.1). Evaluation of the secondary endpoint on day 8 showed improvement of perfusion in 80% of patients treated with LMWH compared with 81% of controls.

Recommendations for clinical practice **This study confirms that, as with deep venous thrombosis, the use of LMWH in acute pulmonary embolism is as safe and effective as standard unfractionated heparin. Advantages of LMWH include the elimination of the need for frequent monitoring and dosage adjustments, ease of administration, and a possible decrease in heparin-induced thrombocytopenia and osteoporosis. The primary disadvantage is that LMWHs cost 10 to 20 times more than unfractionated heparin. In the case of treatment of DVT the cost can be defrayed by avoidance of a hospital admission. Given that we are unlikely to attempt outpatient management of acute pulmonary embolism, the additional cost of LMWH is not justified unless clear advantages over tra-**

ditional therapy with unfractionated heparin are shown in the future, or the increased drug cost is offset by decreased costs of administration and monitoring.

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Dosing Interval with Albuterol MDI for Asthma

Karpel JP, Aldrich TK, Prezant DJ, Guguchev K, Gaitan-Salas A, Pathiparti R. Emergency treatment of acute asthma with albuterol metered-dose inhaler plus holding chamber: how often should treatments be administered? Chest 1997; 112:348-56.

Clinical question **What is the optimal dosing interval for treatment of acute asthma with albuterol delivered by metered-dose inhaler (MDI) plus holding chamber?**

Background Bronchodilator delivery by MDI has been shown to be equivalent to wet nebulizer in the treatment of adults with airflow obstruction and reduces time spent in the emergency department.[1] The optimal dosing interval for treatment of acute asthma exacerbation with an MDI is currently unknown.

Population studied The investigators screened 143 adults between 18 and 55 years of age arriving at one of two urban emergency departments (ED) with acute exacerbation of asthma. Of these, 100 were randomized into the protocol by meeting the following criteria: (1) initial $FEV_1 \leq 60\%$ normal predicted value, (2) < 10 pack-years smoking history, (3) ability to perform pulmonary function tests with maximal effort, and (4) absence of multiple co-morbid factors, including but not limited to pregnancy, clinical evidence of very severe airway obstruction, and requirement for other medications for treatment of acute asthma during the study.

Study design and validity All patients received an initial dose of six puffs of albuterol given 1 minute apart. They were then randomized in a double-blind fashion to one of three treatment groups. Subjects in each group received six additional puffs of either medication or placebo every 30 minutes during the 120-minute protocol. Group 1 received albuterol every 30 minutes, group 2 every 60 minutes, and group 3 every 120 minutes. All participants were instructed and monitored in an identical fashion. Treatment groups were similar, with an overall predominance of women in their 30s, taking multiple asthma medications. Intention-to-treat analysis was applied with the exception of one patient.

Outcomes measured The primary outcome was mean change from baseline FEV_1 over 120 minutes. Vital signs, serum potassium levels, and spontaneously volunteered complaints were also assessed. Length of time in the ED was indirectly measured in terms of need for additional beta-agonists prior to discharge.

Results The authors showed a significant increase in FEV_1 in those receiving albuterol every 30 and 60 minutes compared with every 120 minutes ($P < 0.05$). The 30-minute group benefited over the 60-minute group in a subset of "low responders" (<15% increase in initial FEV_1 at 15 minutes, P not given). Otherwise, the 30- and 60-minute groups were not significantly different with an 80% power to show a difference in FEV_1 of more than 500 mL. This remained true when controlled for degree of initial obstruction ($FEV_1 \leq 40\%$). Vital signs, serum potassium levels, and spontaneously volunteered complaints were not clinically different among groups. There was no significant difference in the number of patients requiring systemic steroids or hospitalization. Nearly twice as many participants of the 120-minute group required additional beta-agonists prior to discharge. Actual additional time spent in the ED was not quantified and it is unclear whether participants were still blinded at this time.

Recommendations for clinical practice **Patients treated for acute asthma with albuterol MDI every 30 or 60 minutes, compared with 120 minutes, had a significant increase in FEV_1. The rate of adverse effects, systemic steroid use, and hospitalization was not different among the three treatment groups. Overall time spent in the ED is an important patient-oriented outcome, but no data were given to assess the clinical significance of the observed difference. Until further information is available, clinicians should treat acute asthma with an albuterol MDI plus holding chamber using a dosing interval of 30 to 60 minutes. In this trial of adults, the number of puffs given per dose was six, but other trials have reported favorable outcomes with doses as low as four.**

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Antibiotics for Acute Maxillary Sinusitis

de Bock GH, Dekker FW, Stolk J, Springer MP, Kievit J, van Houwelingen JC. Antimicrobial treatment in acute maxillary sinusitis: a meta-analysis. J Clin Epidemiol 1997; 50:881-90.

Clinical question **Which antibiotic is most effective and best tolerated in the treatment of acute maxillary sinusitis (AMS)?**

Background The effectiveness of antibiotics in treating acute upper respiratory tract infections, including AMS, remains uncertain; yet, they are routinely prescribed by many clinicians. The purpose of this paper was to analyze pooled data from a variety of studies in order to help clinicians choose the best antimicrobial treatment.

Population studied Studies were only included in the analysis when they provided data on the effectiveness and tolerability of different antibiotics for AMS in otherwise healthy adults (aged 13 years and older).

Study design and validity The authors performed a meta-analysis of 3310 subjects from 16 randomized, blinded, comparative studies selected from a MEDLINE literature search of English and European journals between 1984 and 1995. Only recent studies were included because bacterial resistance to antibiotics used in earlier trials has increased. Antibiotic classes tested included penicillins, cephalosporins, tetracyclines, macrolides, and sulfonamides. Doses used were nearly identical across studies. No placebo-controlled studies were published within the given time frame of this analysis.

This complex study included four subanalyses. First, odds ratios with 95% confidence intervals (CI) were recalculated for each paper to confirm the individual study results. Second, unstratified odds ratios were calculated for the pooled data, using an appropriate statistical procedure. This technique permits calculation of data across different study designs and is useful when data are sparse. Unstratified odds ratios are calculated based on the assumption that subjects (antibiotics) tested in different settings perform similarly, which may not always be the case.

In subsequent steps, studies with similar designs were stratified or grouped together. Finally, studies with similar settings were grouped together. Stratified odds ratios were then calculated from these clusters. The authors increased the stringency of the analysis progressively through each step, with the final step therefore providing the results most applicable to the general population.

Outcomes measured This meta-analysis compared antibiotics with respect to three outcomes: clinical cure, clinical success, and adverse events. The researchers defined clinical cure as resolution of all signs and symptoms. Clinical success included clinical cure, as well as improvement sufficient to eliminate need for further follow-up. The authors included only short-term adverse events severe enough to result in discontinuation of treatment.

Results In the first step of the analysis, only two of the studies provided significant differences. Cefpodoxime resulted in significantly more clinical cures than cefaclor (OR = 2.45; 95% CI, 1.32 to 4.55), and loracarbef led to more clinical success than doxycycline (OR = 3.95; 95% CI, 1.08 to 14.44). Meta-analysis of pooled data before stratification revealed an overall clinical cure rate of 69%, clinical success rate of 92%, and adverse event rate of 2.4%.

The heterogeneity (differences in outcomes) of the various studies weakened the statistical power of the analysis progressively through steps 2, 3, and 4. In the final analysis, only beta-lactamase inhibition was associated with higher clinical cure rates, and this conclusion was shown in only one of the individual studies.

Recommendations for clinical practice **Differences in outcomes between antibiotic treatments of AMS in otherwise healthy adults appear to be small. A randomized, double-blind, placebo-controlled trial published after the completion of this meta-analysis failed to demonstrate effectiveness of antibiotics (amoxicillin) in improving the clinical course of AMS.[1] Both articles thus support the hypothesis that no specific antibiotic is likely to be helpful in most cases of AMS.**

Although most clinicians in the United States currently prescribe antibiotics for AMS, it may be more appropriate to prescribe them only for patients who are more sick or at higher risk for complications. When antibiotics are used, clinicians should choose the least expensive and most convenient agent available. Optimal duration of therapy remains controversial and was not addressed in this paper.

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Thrombolytic Therapy for Acute Ischemic Stroke

Wardlaw JM, Warlow CP, Counsell C. Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke. Lancet 1997; 350:607-14.

Clinical question **Does thrombolytic therapy change the outcome of acute ischemic stroke?**

Background Randomized controlled trials of thrombolysis in acute ischemic stroke have produced variable results. Nonetheless, on the basis of the National Institute of Neurological Disorders and Stroke (NINDS) trial. the United States Food and Drug Administration has licensed tissue-plasminogen activator (t-PA) for use within 3 hours of onset of an acute ischemic stroke. This systematic review presents the data from 12 randomized controlled trials on the use of thrombolysis for acute ischemic stroke, allowing clinicians to make the best-informed decision about the use of this controversial therapy.

Population studied Study patients were those diagnosed with an acute ischemic stroke by CT or MR scan. Individual trials varied in the type of ischemic stroke (presumed noncardioembolic ischemic stroke, cardioembolic stroke with angiographic occlusion, large carotid territory infarcts, or any ischemic stroke), patient age (upper age limit between 50 and 85 years of age, or no age limit), and time from stroke onset to symptoms (3 hours to 2 weeks).

Study design and validity The authors performed an extensive search of the published literature using multiple strategies and also contacted investigators for unpublished data. Randomized trials were included if the investigators were blinded to the treatment at its outset, if the study groups differed only with the treatment of interest, and if the trials could be analyzed on an intention-to-treat basis. Any trial that did not adequately account for patient follow-up was excluded. There were comparable control groups for each study, but there was significant variation between studies in baseline case fatality rates (2% to 38%). Follow-up varied from 1 to 6 months.

Tabular data were gathered for individual studies and then aggregated by type of thrombolytic (urokinase, streptokinase, t-PA) and overall. Outcomes were presented for individual studies and for aggregated data. Univariate subgroup analyses examined factors such as the effect of time to treatment and thrombolytic drug dose, but multivariate analyses were not possible due to an insufficient number of trials. Individual patient data were not available for a majority of the studies, further limiting analyses.

Outcomes measured The primary outcome was the composite of death or dependency for activities of daily living at the end of follow-up. Other outcomes included the development of a symptomatic intracranial hemorrhage and early and total case fatality.

Results Twelve trials with 3435 patients met the inclusion criteria. Three trials used urokinase, four streptokinase, and five t-PA. The aggregate study data showed a 6.5% absolute reduction in risk of death or dependency with thrombolysis (61.5% with treatment, 68.0% for controls). This benefit correlated with 65 fewer dead or dependent patients per 1000 treated (95% CI, 28 to 107), and 1 dead or dependent patient averted for every 15 patients treated (NNT = 15). However, there were significant increases in early death for those patients in the treatment group (extra 91 deaths in the first 2 weeks per 1000 treated patients; 1 early death for every 11 patients treated), total case fatality (extra 37 deaths per 1000 patients treated; 1 early death for every 29 patients treated), and symptomatic or fatal intracranial hemorrhage (extra 70 intracranial hemorrhages per 1000 treated patients; 1 intracranial hemorrhage for every 14 patients treated).

Exploratory analyses provided some evidence that trials randomizing patients within 3 hours had lower death rates than those randomizing later, and that trials concomitantly using antiplatelet agents (aspirin, for example) had higher death rates than those not using these agents.

Recommendations for clinical practice **This study suggests that thrombolytic therapy in acute ischemic stroke may decrease the combined outcome of death or dependency, but carries substantial risk, including increased death and symptomatic intracranial hemorrhage. A number of questions remain unanswered, including the characteristics of patients most likely to benefit or be harmed by thrombolytic therapy, the type and dose of drug, and the true time-window for treatment. Since most stroke patients are unlikely to reach the hospital and receive a CT or MR scan within 3 hours, few patients would even qualify for the use of thrombolysis. For those patients who meet the criteria for use of thrombolysis, clinicians must provide full disclosure of the risks, as well as potential benefits, of this controversial therapy. This study provides insufficient evidence to recommend that clinicians routinely use thrombolysis in acute ischemic stroke.**

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Compression Treatment for Venous Leg Ulcers

Fletcher A, Cullum N, Sheldon TA. A systematic review of compression treatment for venous leg ulcers. BMJ 1997; 315:576-80.

Clinical question **Is an Unna's boot or other methods of compression more effective than simple dressing for treating venous leg ulcers?**

Background Venous stasis ulcer is a problem commonly treated on an outpatient basis by family physicians. There are geographic variations in the treatment of this disorder. In the United States, the most commonly recommended treatment is the application of an Unna's boot, while in the United Kingdom multilayer elastic compression is the most common treatment. In Europe, the standard treatment is the inelastic, short-stretch bandage.[1] After resolution of the ulcer, some form of compressive stocking is ordered to prevent recurrence of the ulcer.

Population studied The data source for this study was randomized clinical trials of compression treatment. A review of ten of the original articles revealed that the studies were performed in specialty outpatient sites (dermatology, general surgery, vascular surgery, dedicated wound clinics). This raises the potential of referral bias, since patients referred to these settings may have a long-standing or more severe disease than those encountered in primary care practice.

Study design and validity This study addresses all of the important characteristics of a well-done systematic review and meta-analysis. A well-defined question was posed. An electronic search of 19 databases was conducted. The authors also identified studies through hand searching, reviewing citations of identified studies, and contacting manufacturers and original authors to uncover unpublished studies. Studies were reviewed and abstracted by two reviewers. When applicable, a fixed-effects model was used to pool the results of homogeneous studies.

Outcomes measured Primary outcomes were the rate of healing and the proportion of patients with venous ulcers healed in a specified period of time.

Results Compression led to a greater number of patients with healed ulcers. There was conflicting evidence regarding the most effective type of compression (elastic or inelastic), although high-compression treatment appeared to be more effective than low-compression. Pooled data showed that multilayer elastic high-compression treatment was more effective than single layer (OR = 2.2, 95% CI, 1.3 to 3.5). There was no difference between different medium- and high-compression treatments. Finally, pooling of data from two small trials showed that the addition of intermittent pneumatic compression to compression stockings or an Unna's boot is beneficial (OR = 10.0, 95% CI, 3.0 to 33.8). The authors felt that the overall quality of research in this area was poor because of small sample sizes, inadequate follow-up periods, and because recurrence of ulcers was rarely considered. No cost or utility (quality of life) data were reported.

Recommendations for clinical practice **This study confirms what we have been taught for years: An Unna's boot is an effective treatment for venous leg ulcers. Other types of compression are also effective, but which style of compression is more effective or less expensive has not been determined.**

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Calcium and Vitamin D Supplements for Elderly Patients

Dawson-Hughes B, Harris SS, Krall EA, and Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337:670-6.

Clinical question **Does supplementation with calcium and vitamin D reduce the incidence of fractures in community-dwelling men and women 65 years of age or older?**

Background Osteoporotic fractures are a major source of morbidity for elderly Americans. Previous studies have shown a benefit from calcium and vitamin D supplementation in middle-aged postmenopausal women, as well as in elderly women in a retirement home setting. This study was designed to evaluate the effect of combined vitamin D and calcium supplementation on elderly women and men in an ambulatory setting.

Population studied Investigators recruited 848 healthy, ambulatory men and women 65 years of age or older using direct mailings and community presentations. After prescreening with a questionnaire, 545 were invited for further participation. Of those, 51 were excluded and 49 chose not to participate. Exclusion criteria included current cancer or hyperparathyroidism; recent nephrolithiasis; a history of renal disease or bilat-

eral hip surgery; laboratory evidence of liver or kidney disease; and therapy with estrogen, a bisphosphonate, calcitonin, tamoxifen, or testosterone. Dietary calcium intake had to be <1500 mg/day. Study subjects included 199 men and 246 women and the population was almost entirely white.

Study design and validity Participants were randomized in a double-blind fashion to take daily supplements of calcium (500 mg) and vitamin D (700 IU) or placebo. Randomization was stratified to account for sex, race, and decade of age. Of the 127 subjects not completing the study protocol, more than half (71) were included in the final analysis in an intention-to-treat fashion. Patients not completing the entire protocol did not differ from the rest of the study group in baseline characteristics. Compliance with treatment, measured by pill count, was estimated at 92%. The study period lasted 3 years, with evaluations every 6 months and as needed following traumatic events. Fractures were confirmed using radiographs in all but one case.

Outcomes measured The primary outcomes measured were bone mineral density (BMD) and nonvertebral fractures. Secondary outcomes included several biochemical measures of bone metabolism.

Results A statistically significant improvement was noted in total body BMD in both male and female groups compared with placebo (P <0.001). Separate measurements of the femoral neck and spine failed to show, however, any significant improvement in BMD in women (P = 0.7 and 0.3, respectively). Patients treated with calcium and vitamin D also had greater improvements in a number of biochemical markers of bone metabolism. There were 37 total fractures during the study period, including 11 in the treatment group compared with 26 in the placebo group (relative risk, 0.5; 95% CI, 0.2 to 0.9). Only two fractures occurred in male subjects, both in the placebo group. The treatment was generally well tolerated with only 20 subjects discontinuing treatment.

Recommendations for clinical practice **A clinically relevant reduction in nonvertebral fracture rates can be achieved using calcium (500 mg daily) and vitamin D supplementation (700 IU daily) in the outpatient setting in elderly, white women not currently taking estrogen replacement. Treatment benefit was seen with much lower doses of calcium than had been used in other studies. An earlier study using lower doses of vitamin D alone (400 IU) was unable to show a reduction in the incidence of fractures. The low incidence of fractures among men in this study prevents any conclusions regarding the utility of this intervention in elderly men. There is no evidence to suggest that these results are generalizable to nonwhite populations. It remains uncertain whether there is a clinically relevant incremental benefit of calcium and vitamin D in women already using estrogen. The other known benefits of estrogen replacement therapy continue to justify its use as the first-line agent for the treatment and prevention of osteoporosis and related fractures.**

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