ACE inhibitors prevent stroke in high-risk patients, independent of blood pressure-lowering effect


**BACKGROUND** Studies have shown that strokes can be prevented by lowering blood pressure in hypertensive patients. Recent experimental and human data suggest that angiotensin-converting enzyme (ACE) inhibitors may lower ischemic vascular events independent of lowering blood pressure. This report evaluated the effect of ramipril on the incidence and severity of strokes in a population at high risk for cardiovascular events with a wide range of blood pressures.

**POPULATION STUDIED** This report is a secondary analysis of data from the HOPE study, a double-blind randomized trial of ramipril, vitamin E, or the combination in patients at high risk for cardiovascular events. The 9297 patients in this study were all 55 years of age or older and had a history of vascular disease (coronary artery, peripheral, or cerebrovascular) or diabetes plus at least 1 other cardiovascular risk factor. Patients were excluded if they were taking either an ACE inhibitor or vitamin E; had heart failure or a known left ventricular ejection fraction of less than 40%; known proteinuria; untreated hypertension; or a previous stroke or myocardial infarction less than 1 month before enrollment. The patients had an average blood pressure of 139/79 mm Hg, although 46% had mild, previously undiagnosed hypertension.

**STUDY DESIGN AND VALIDITY** In the HOPE study, patients were randomized to receive up to 10 mg ramipril daily, 400 IU vitamin E, or no treatment. Placebos were used in the control group. Average follow-up was 4.5 years. Patients were followed for residual cognitive or functional impairment. The original study was not specifically designed to address the question of stroke prevention, but the sample size of more than 9000 patients provides acceptable power for most comparisons of clinical significance.

**OUTCOMES MEASURED** The primary outcome was the occurrence of stroke or transient ischemic attacks (TIAs). Symptoms and functional impairment were recorded for every stroke. Blood pressure was also measured at enrollment, after 2 years, and at the end of the study.

**RESULTS** The relative risk (RR) of any stroke was reduced by 32% (3.4% vs 4.9%) in the ramipril group compared with the placebo group (RR = 0.68; 95% confidence interval [CI], 0.56–0.84). This reduction translates into a number needed to treat (NNT) of 67; ie, 1 stroke would be prevented over 4.5 years for every 67 patients treated with ramipril instead of placebo. Fatal stroke was reduced 61% (0.4% vs 1.0%) with ramipril treatment (RR = 0.39; 95% CI, 0.22–0.67), with an NNT of 166 for 4.5 years. Nonfatal stroke was reduced 24% (3.0% vs 3.9%) with ramipril treatment (RR = 0.76; 95% CI, 0.61–0.94), with an NNT of 111. The relative risk of a TIA was reduced 17% (4.1% vs 4.9%) with ramipril treatment (0.83; 95% CI, 0.68–1.00; \( P = .052 \)), with an NNT of 125. Overall, patients taking ramipril had a significantly reduced combined risk of stroke and TIA of 23% (6.8% vs 8.7%) compared with placebo (RR = 0.77; 95% CI, 0.66–0.89; \( P = .0004 \)). The NNT for the combined end point was 53. Additionally, patients who experienced a stroke despite treatment were less likely to have residual cognitive or functional impairment. These benefits were consistent across baseline blood pressures and subgroups of cardiovascular risk factors. ACE inhibitor treatment reduced systolic blood pressure by an average of 3.8 mm Hg and diastolic blood pressure by an average of 2.8 mm Hg.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**
Treating older patients at high risk of stroke with the ACE inhibitor ramipril reduces their risk of experiencing fatal and nonfatal stroke and TIA. This beneficial effect is independent of blood pressure. Patients with preexisting vascular disease or diabetes and other cardiovascular risk factors should be placed on an ACE inhibitor regardless of their blood pressure.

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Each month, the POEMs editorial team reviews more than 90 journals of interest to primary care physicians, and identifies articles you need to know about to stay up to date. We call these articles POEMs (Patient-Oriented Evidence that Matters) because they address common primary care problems, report outcomes that matter to patients, and, if valid, require us to change the way we practice. The collected reviews are available online at www.jfponline.com.
Intravenous albuterol effective for acute severe asthma


**BACKGROUND** Bolus intravenous (IV) albuterol (salbutamol) improved outcomes in pediatric patients with severe asthma exacerbations in 1 earlier small study. Previous studies demonstrated that the addition of nebulized ipratropium bromide to initial emergency department therapy improves pulmonary function, but it is unclear whether combining the therapies results in earlier hospital discharge. This study compared these 2 approaches to determine their relative benefit in children with acute severe asthma.

**POPULATION STUDIED** The researchers studied 55 children (aged 1–14 years) presenting with severe acute asthma to the emergency department of a tertiary children’s hospital in Sydney, Australia. Children were classified as having severe asthma if they had all 4 features of respiratory distress (wheezing, sternal retraction, accessory muscle use, and dyspnea) or had any of the absolute criteria (cyanosis, pulsus paradoxus, altered consciousness, or a silent chest auscultation). Baseline demographics and clinical characteristics were similar. Children who were excluded included those with life-threatening asthma, age younger than 12 months, presence of heart disease, family history of Wolff-Parkinson-White or supraventricular tachycardia, other respiratory disease, or pneumonia, and those who had received inhaled ipratropium bromide that day.

**STUDY DESIGN AND VALIDITY** This was a randomized, double-blind, double-dummy trial. The enrolling physician, treating physician, and assessor of outcome were all blinded. All children received 1 dose of nebulized albuterol 2.5 or 5 mg, then were assessed for asthma severity. Children meeting inclusion criteria received oxygen as needed, 1 mg/kg IV bolus methylprednisolone, and nebulized albuterol every 20 minutes for the first hour. The frequency of nebulized albuterol was then decreased based on clinical improvement. Patients were then randomized to receive IV albuterol (15 µg/kg); IV saline and inhaled ipratropium bromide (250 mg) every 20 minutes; or IV albuterol (15 µg/kg) and inhaled ipratropium bromide (250 µg) every 20 minutes. Asthma severity was assessed at 1 and 2 hours into the study using the clinical assessment scale and pulmonary index score. All 55 children completed the study.

**OUTCOMES MEASURED** The primary outcomes for this study were mean recovery time (time from randomization to when patients no longer needed nebulized albuterol of a given frequency) and mean discharge time from the hospital. Secondary outcomes included clinical signs of moderate to severe asthma 2 hours after randomization and incidence of medication-related side effects.

**RESULTS** Children treated with IV albuterol showed a significant benefit over those treated with inhaled ipratropium in recovery at 90, 120, and 180 minutes (P = .007, .01, and .004, respectively). Children in the IV albuterol group were ready for discharge 28.0 hours earlier than those in the ipratropium group (48.3 vs 76.3 hours; P = .005). The combination of IV albuterol and ipratropium showed a significant benefit over ipratropium alone in recovery at 90 and 120 minutes (P = .02 and .008, respectively). However, no significant difference was evident between the combination and ipratropium alone in time to discharge (57.6 vs 76.3 hours, respectively; P = .2). The combination demonstrated no significant benefit over IV albuterol for any outcome. No significant adverse effects were documented in any of the patients, including tachycardia of more than 200 beats per minute for at least 5 minutes.

**RECOMMENDATIONS FOR CLINICAL PRACTICE** In children with severe acute asthma, IV albuterol (15 µg/kg) in addition to nebulized albuterol and IV methylprednisolone, resulted in more rapid improvement of symptoms and decreased length of stay as compared with the use of nebulized ipratropium. However, because IV albuterol is not available in the United States and a Cochrane Database Review1 concluded there is no evidence to support use of IV β2-agonists in patients with severe asthma, larger trials need to be conducted to determine the place in therapy for IV albuterol.

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**REFERENCE**

Albuterol via metered-dose inhaler and nebulizer equivalent in adults


- **BACKGROUND** Historically, nebulizers have been preferred over metered-dose inhalers (MDIs) for the treatment of asthma exacerbations, although numerous studies have shown their equivalence. A systematic review of 21 randomized trials supported the equivalence of an MDI with spacer and a nebulizer; the method of albuterol delivery did not affect hospital admission rates, length of stay in the emergency department, or measures of pulmonary function. Advantages of MDIs may include lower costs, less excess drug exposure, and easier use for patients and physicians.

- **POPULATION STUDIED** The study population consisted of all patients older than 18 years who presented to an emergency department over a 2.5-year period with an asthma exacerbation (2342 visits, 1429 patients). Most patients were African American (75.4%). Most were women (58.6%), and the mean age was 35.5 ± 13.5 years.

- **STUDY DESIGN AND VALIDITY** The study was a large, prospective, unblinded, and nonrandomized trial consisting of 2 phases. For the first 12 months, physicians, using standard National Institutes of Health guidelines, began treatment with a nebulizer (913 visits). Then for the next 18 months, physicians began treatment with albuterol delivered via MDI and spacer (1429 visits). The dose was 5 puffs, then 3 to 5 puffs every 20 minutes as needed. At the time of discharge from the emergency department during the MDI phase of the study, patients received a peak flow meter, an MDI and spacer, an inhaled corticosteroid, written materials, and counseling by emergency department nurses.

This study was fairly weak. It was not randomized or blinded, and the patient population could have differed between the 2 phases of the study, although measurement of demographic characteristics and pre-albuterol peak expiratory flow rate (PEFR) and oxygen saturation level (SaO2) revealed that the study groups were comparable. Because extent of breathing difficulty was not assessed, it is unknown if study results apply to patients with severe asthma. Moreover, physicians broke protocol by using nebulizers in 22.6% of the patients in the MDI phase if the physicians thought the treatment would benefit the patient’s physical or mental status. In addition to different routes of administration of albuterol, the intervention also differed in that inhaled steroids were given in the MDI-treated group but not the nebulizer-treated patients. This intervention could have contributed to the decreased relapse rate seen in the MDI-treated group.

- **OUTCOMES MEASURED** The outcomes measured were PEFR, SaO2, heart and respiratory rates, total albuterol dose, and the more patient-oriented outcomes of rate of hospital admission, relapse rate, time in the emergency department, and costs.

- **RESULTS** In the MDI phase, post-albuterol PEFR was 11.0% higher (342 L/min vs 308 L/min; \( P = .001 \)) and change in PEFR was 13.3% higher (127 L/min vs 112 L/min; \( P = .002 \)). Change in SaO2 was significant \( (P = .043) \), and the total albuterol dose was significantly less in the MDI group \( (1125 \mu g \text{ vs } 6700 \mu g; \ P = .001) \). However, these differences did not result in significantly lower hospital admission rates. Relapse rates were significantly lower at both 14 and 21 days in the MDI phase \( (6.6\% \text{ and } 10.7\% \text{ vs } 9.6\% \text{ and } 13.5\%; \ P < .01 \text{ and } P < .05) \). Patients treated with MDIs spent 6.5% less time in the emergency department \( (163.6 \text{ min vs } 175.0 \text{ min}; \ P = .007) \). The difference in visit charges was not significant.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**
This study is yet another to show that delivery of albuterol by MDI and spacer is as effective as delivery by nebulizer in adults with asthma presenting to the emergency department. Patients treated with an MDI and spacer had greater improvement in peak flow, and hospital admission rates did not differ. This trial was not well designed, but its results echo the many other studies, using tighter methods, that show equivalence. Although there may be some patients and practice situations for which the nebulizer is preferred, the MDI and spacer can safely be a first-line treatment much of the time. Incorporating MDI use in the treatment of acute asthma exacerbations may help dispel the misconception of many patients that the nebulizer is a more “powerful” way of treating asthma.

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**REFERENCE**
Utility of Factor V Leiden testing for idiopathic venous thromboembolism is unclear


- BACKGROUND Factor V Leiden deficiency is associated with an increased risk of initial venous thromboembolism. The prevalence of Factor V Leiden deficiency varies with ethnicity and age of onset of initial venous thromboembolism. If Factor V Leiden deficiency predicts recurrent venous thromboembolism, putting affected patients on extended anticoagulation therapy may be beneficial. This study evaluated the cost effectiveness of testing patients for Factor V Leiden deficiency after initial venous thromboembolism, taking into account costs and complications associated with recurrent venous thromboembolism, compared with ongoing anticoagulation therapy.

- POPULATION STUDIED This study was a decision analysis that assumed a base case of a 35-year-old woman with initial venous thromboembolism. Subpopulations for sensitivity analyses were based on ethnicity, prevalence of Factor V Leiden deficiency, age at onset, precipitating factors for venous thromboembolism, length of therapeutic intervention, and morbidities attributed to anticoagulation. The risk for recurrent venous thromboembolism in patients homozygous for Factor V Leiden deficiency is high; this study focused on heterozygotes, a population whose recurrence risk is less well defined.

- STUDY DESIGN AND VALIDITY This decision analysis used sound methods and the sensitivity analyses were appropriate. It is unclear whether a systematic literature review was performed. A pivotal factor was the assumption of an increased risk of recurrence in patients with Factor V Leiden deficiency as compared with patients without the deficiency. The authors based this assumption on an 8-year study that showed an increased risk of recurrence of 2.4 (95% confidence interval [CI], 1.3–4.5, n = 41). All of the recurrences were detected in the first 3 years. However, other studies, of somewhat shorter duration, demonstrated risk ratios of 1.1 (95% CI, 0.7–1.6, n = 112) within 4 years1 and 0.5 (95% CI, 0.1–1.8, n = 37) within 2 years.2

- OUTCOMES MEASURED The primary outcomes reported were the risk of recurrence of deep venous thrombosis, morbidity associated with therapeutic intervention, and the cost effectiveness of 3 different treatment strategies.

- RESULTS All Factor V Leiden-deficient patients were assumed to have a 7.4% per-year risk of recurrence. Various models were constructed based on the duration of that increased risk. The base case assumed a 0% recurrent deep venous thrombosis risk after 3 years; the modified-base case strategy assumed that patients returned to the population average of 2.3% per year after 3 years; and the constant rate model assumed a continued 7.4% per-year risk of recurrent deep venous thrombosis. In all models, testing and treating for life was most expensive. The base and modified-base models demonstrated testing and treatment for 3 years were the most cost effective. If a patient population has a risk of major hemorrhage of more than 1.9% per year, a low prevalence of Factor V Leiden deficiency, a clear precipitant for venous thromboembolism, or a recurrence risk for venous thromboembolism from Factor V Leiden deficiency of less than 1.9, then testing is not indicated.

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REFERENCES
Losartan more effective than atenolol in hypertension with left ventricular hypertrophy


- **BACKGROUND** Left ventricular hypertrophy may be responsible for the higher risk of cardiovascular events that hypertensive patients suffer even after blood pressure reduction. Because angiotensin II is associated with the development of left ventricular hypertrophy, selective blockade of angiotensin II may reverse the hypertrophy and lead to decreased cardiovascular morbidity beyond just lowering blood pressure.

- **POPULATION STUDIED** A total of 9193 adults, aged 55 to 80 years, with hypertension (previously treated or untreated) and electrocardiographic (ECG) evidence of left ventricular hypertrophy were enrolled in the trial. Study participants were from Northern Europe and the United States; 54% were female and 92% were white. Patients with secondary hypertension, heart failure or left ventricular ejection fraction of 40% or less, history of myocardial infarction (MI) or stroke within the last 6 months, or angina pectoris requiring beta-blockers or calcium channel blockers were excluded. Also excluded were patients with disorders that required treatment with losartan or other angiotensin II type 1-receptor blockers, atenolol or other beta-blockers, hydrochlorothiazide, or angiotensin-converting enzyme (ACE) inhibitors.

- **STUDY DESIGN AND VALIDITY** After a run-in period with placebo, 9222 patients were randomized in a double-blind fashion to receive either losartan (50 mg daily) or atenolol (50 mg daily). Of these, 29 patients were excluded prior to group assignment and the remaining 9193 were included in an intention-to-treat analysis. The authors did not specifically state whether the treatment allocation process was concealed. In addition to either losartan or atenolol, patients were treated with hydrochlorothiazide and other antihypertensive medications as needed to obtain a blood pressure goal of less than 140/90 mm Hg. An independent clinical committee blinded to treatment group assignment determined the validity of all cardiovascular end points.

  Two percent (n = 197) of patients dropped out of the study, in roughly equal numbers from each treatment group. Patients were followed for at least 4 years (average 4.8 years). A monitoring committee terminated the study when an adequate number of cardiovascular events had occurred.

- **OUTCOMES MEASURED** The primary end point was cardiovascular morbidity and death, a composite end point consisting of stroke, MI, or cardiovascular death. The authors also measured individual cardiovascular events (stroke, MI, death) separately. Extensive data on blood pressure, use of additional medications, changes in ECG evidence of left ventricular hypertrophy, and adverse events were also compared.

- **RESULTS** Treatment groups had similar demographics, including baseline vital signs, ECG findings, cardiovascular risk scores, and mean arterial blood pressure on treatment. Patients in the losartan group had a significantly lower relative risk (RR) of the composite end point (stroke, MI, or cardiovascular death; RR = 0.87; 95% confidence interval [CI], 0.77–0.98; numbers needed to treat [NNT] = 244 patients per year). On individual outcomes, patients in the losartan group had a reduced risk of stroke (RR = 0.75; 95% CI, 0.63–0.89), but no statistically significant reduction in cardiovascular mortality (RR = 0.89; 95% CI, 0.73–0.97), MI (RR = 1.07; 95% CI, 0.88–1.31) or all-cause mortality (RR = 0.90; 95% CI, 0.78–1.03).

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Losartan may reduce cardiovascular morbidity and related deaths in hypertensive patients with documented left ventricular hypertrophy beyond that expected from only lowering blood pressure, especially through a reduction in stroke risk. However, this benefit was small in a select group of patients and no additional reduction was demonstrated in all-cause mortality compared with less expensive atenolol. The benefit of losartan over atenolol was more pronounced in a separate trial of hypertensive diabetic patients with left ventricular hypertrophy (NNT = 122 patients per year). Losartan was previously shown to be inferior to an ACE inhibitor agent (captopril) in the treatment of heart failure. Thus, there is no reason to believe that the benefit of losartan shown in this study is superior to (and may actually be less than) that of less expensive ACE inhibitors.

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**REFERENCES**


Caution necessary when interpreting results of outpatient endometrial sampling
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BACKGROUND Outpatient endometrial sampling in symptomatic women with abnormal vaginal bleeding is a common practice in primary care. Results from existing studies evaluating various outpatient office-based endometrial sampling techniques are inconsistent.

POPULATION STUDIED The goal of this systematic quantitative review of the published literature was to determine the accuracy of outpatient endometrial biopsy in detecting endometrial cancer. The authors searched general bibliographic databases (MEDLINE and EMBASE) without language restrictions from 1980 through 1999 for articles comparing outpatient endometrial biopsy results with a reference (gold) standard (most commonly dilation and curettage, hysterectomy, or guided biopsy). Of 1369 trials initially screened, only 11 that were either prospective observational or comparative cross-sectional studies met the inclusion criteria. These 11 trials enrolled a total of 1013 pre- and postmenopausal women with abnormal uterine bleeding; postmenopausal women represented nearly 80% of the study subjects. No additional patient information was reported. The prevalence of endometrial cancer in the study population was 6.3%.

STUDY DESIGN AND VALIDITY The small number and poor quality of the existing studies significantly limited this analysis. Two authors independently reviewed the studies for inclusion, and disagreement was resolved by consensus or arbitration by a third reviewer. Prospective and consecutive recruitment of eligible women were considered adequate for inclusion, whereas convenience sampling was considered inadequate. Blinding was considered adequate if the pathologists providing gold standard histological diagnoses were unaware of the results of the outpatient biopsy and inadequate if they were aware of the results. A decision to perform a reference test only in response to the results of an outpatient biopsy was considered inadequate.

Seven of the 11 selected studies enrolled nonconsecutive patients and only 2 of the 11 studies reported that outcomes were assessed blindly; blinding was not reported by the other studies. The nonblinding of pathologists interpreting the reference standards may have overinflated the sensitivities reported in the individual trials and thus biased the overall positive likelihood ratio(s) of the individual and combined sampling techniques.

In this review, only results from studies evaluating the Pipelle outpatient device have adequate numbers of patients included to make a valid assessment, although the authors provided combined data on all the devices used as well. A funnel plot evaluation of the included studies found little evidence for publication bias.

OUTCOMES MEASURED The primary outcome measure was the accuracy with which endometrial cancer was diagnosed by the various sampling techniques. Secondary outcomes were device failures and rates of inadequate specimens.

RESULTS The pooled likelihood ratios for endometrial cancer using the Pipelle outpatient device with adequate endometrial sampling were 64.6 (95% confidence interval [CI], 22.3–187.1) for positive results and 0.1 (95% CI, 0.04–0.28) for negative results. The posttest probability given the initial prevalence of 6.3% with a positive outpatient test was 81.3% (95% CI, 52.4–94.4) and decreased to 0.7% (95% CI, 0.2–2.4) for a negative test. Inadequate samples were considered as negative results, which increased the accuracy. The overall failure rate (inability to perform the procedure for one reason or another) for outpatient biopsy was 7%.

Three endometrial cancers were missed with adequate endometrial samples and 1 cancer with an inadequate sample (false-negative rate = 0.4%). The pretest probability (prevalence) of endometrial cancer for all women in the study was 6.3%, which is lower than the commonly reported prevalence of 15% in postmenopausal women with abnormal vaginal bleeding. An increased pretest probability increases the false-negative rate, making a negative result less reliable.

RECOMMENDATIONS FOR CLINICAL PRACTICE Caution is necessary when using office-based endometrial sampling techniques, including the Pipelle, to evaluate women with abnormal uterine bleeding. An abnormal histological finding is highly accurate and likely to represent true disease. Negative results, including inadequate sampling, must be interpreted with caution, because the false-negative rate for excluding endometrial cancer reported in this analysis was 4/1000 women sampled. Many clinicians and their patients may find this false-negative rate clinically unacceptable, while others may find reassurance from a “low-risk” assessment. In cases of abnormal uterine bleeding in which symptoms persist despite a negative biopsy, further evaluation and input from individual patients is recommended.

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Hemoccult tests are insensitive for upper gastrointestinal cancer

- **BACKGROUND** Fecal occult blood (Hemoccult) screening followed by colonoscopy has been shown to reduce colon cancer mortality, but uncertainty remains about the utility of upper endoscopy in further evaluation of patients with positive Hemoccult testing. This study addressed the risk of upper gastrointestinal cancer in patients whose Hemoccult test results are positive.

- **POPULATION STUDIED** The researchers used a cohort of 61,933 people aged 45 to 75 years in a defined region of Denmark who were followed from 1985 through 2000. They excluded patients with known colorectal neoplasia and distant metastases. The results from this population are likely to apply to the usual US family practice, although the researchers did not provide information about age distribution, dietary habits, alcohol or tobacco history, cancer history, or ethnicity, factors that may influence the development of upper gastrointestinal cancers.

- **STUDY DESIGN AND VALIDITY** Subjects were drawn from the screening arm of a population-based randomized trial of colon cancer screening. A total of 30,967 patients were offered the screening. After education about diet and medications, subjects were given nonrehydrated fecal occult blood tests biennially. Patients with positive Hemoccult tests were interviewed and examined, and underwent colonoscopy or double-contrast enema; those with carcinoma and/or adenoma were enrolled in a surveillance program. Upper endoscopy and other studies were performed only if warranted by symptoms. The county databases, supplemented by death certificates, the Danish National Register of Patients, and the National Cancer Register, were used to obtain information about malignant disease. Upper gastrointestinal cancers were defined as cancer of the esophagus, stomach, small intestine, and biliary and pancreatic systems. The sensitivity and positive predictive values of Hemoccult testing were calculated using all upper gastrointestinal cancers developing within 2 years.

The overall methodology of this study was strong. The longitudinal data from the Danish National Registries was of good quality and likely captured almost all cancers; the trial design also allowed prospective assessment of symptoms and hemoglobin level. A minor weakness was the use of a 2-year interval for detection of upper gastrointestinal cancers—for some cancers, the lead time is probably longer, possibly leading to a small underestimation of the likelihood of cancer developing. Another relative weakness was the lack of control for confounding factors such as diet, ethnicity, and alcohol/tobacco use that might increase the risk of upper gastrointestinal cancers in some populations of patients.

- **OUTCOMES MEASURED** The primary outcomes were the sensitivity and positive predictive value of the Hemoccult test with respect to upper gastrointestinal cancer. Cost, patient and physician satisfaction, and impact on quality of life were not addressed.

- **RESULTS** From 1985 through 2000, 473 patients were diagnosed with upper gastrointestinal cancer in the overall study population, 199 of whom had upper gastrointestinal cancer diagnosed within 2 years of a negative fecal occult test. The sensitivity and positive predictive value of fecal occult blood for upper gastrointestinal cancers diagnosed within 2 years of a positive test were 4.8% and 0.57%, respectively. The presence of symptoms or anemia did not improve the performance of fecal occult blood as a screening test for upper gastrointestinal cancers.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**
This study provides good evidence that patients with positive fecal occult blood testing have a low risk of upper gastrointestinal cancer. Clinicians should not routinely perform upper endoscopy to screen for cancer in patients whose Hemoccult test is positive. The presence of symptoms or anemia does not improve the performance of fecal occult blood as a diagnostic test, but clinicians should continue to evaluate symptoms carefully and order additional studies accordingly.

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Homeopathy ineffective for asthma

- **BACKGROUND** Many individuals with asthma are allergic to house dust mites. The incidence and severity of asthma is increasing. More people are seeking complementary medical care, including homeopathy. Homeopathy attempts to mitigate disease by diluting the treatment without diluting the effect.

- **POPULATION STUDIED** The investigators recruited 1000 asthmatic outpatients from 38 general practices in Hampshire and Dorset, England. Of these, 327 tested positive for house dust mite allergy. Eighty-five patients were excluded for asthma that was either too mild or too well-controlled. Thus 242 subjects between 18 and 55 years old were randomized into the study. This group included both sexes; no note was made of race.

- **STUDY DESIGN AND VALIDITY** A double-blind, randomized control design was used. A French manufacturer of homeopathic products prepared the active agent by making 30 sequential 1:100 dilutions of a house dust mite allergen (this “ultramolecular” is a highly diluted solution of allergen molecules). After a 4-week period to assess baseline symptoms, subjects were randomized to receive either an oral homeopathic immunotherapy preparation or a similarly prepared placebo in 3 doses over 24 hours. They were then followed for 16 weeks with 3 clinic visits and every-other-week symptom diaries.

  This study was well designed. The research pharmacist, the clinicians, and the patients were all blinded to the preparations. The study had concealed allocation, intention-to-treat analysis, and 100% follow-up. Approximately equal numbers from each group were withdrawn for asthma exacerbations requiring steroids, protocol violations, concurrent illnesses, or patient preference. The study had a power of 80% to detect significant differences in the primary outcome measurements.

- **OUTCOMES MEASURED** Primary outcomes were change in lung function as measured by forced expiratory volume in 1 second (FEV₁) and quality of life as measured by proportion of symptom-free days in each 7-day diary period. Other outcomes included peak expiratory flow, scores for asthma visual analogue scale, and average mood scores.

- **RESULTS** This homeopathic therapy showed no significant improvement over placebo with regard to FEV₁ (0.136 L/sec active agent vs 0.414 L/sec placebo, 95% confidence interval [CI] =0.136–0.693) or mean improvement in quality of life (0.090 active agent vs 0.117 placebo, 95% CI = –0.096 to 0.0150). Neither was there any significant difference in any of the secondary outcomes. These results were independent of the subjects’ belief in complementary medicine. Interestingly, at different times during the study improvement was noted in both the active therapy and placebo groups in FEV₁, quality of life, and mood.

- **RECOMMENDATIONS FOR CLINICAL PRACTICE** This oral homeopathic immunotherapy neither decreased symptoms nor improved lung function over placebo in treatment of house dust mite allergy in asthmatic individuals. Based on this well-done trial, this therapy cannot be recommended for such patients. Because this was a placebo trial and showed no benefit, homeopathic immunotherapy should not be substituted for other efficacious pharmacological agents in the treatment of asthma.

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