POEMs

Patient-Oriented Evidence that Matters

Each month, the POEMs editorial team reviews over 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 over 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

IM Diclofenac for Biliary Colic

Reference Akriviadis EA, Hatzigavriel M, Kapnias D, et al. Treatment of biliary colic with diclofenac: a randomized, double-blind, placebo-controlled study. Gastroenterology 1997; 113:225-31.

Clinical question **Does intramuscular diclofenac relieve pain from biliary colic and prevent short-term complications of cholelithiasis?**

Background Nonsteroidal anti-inflammatory drugs (NSAIDs) are clearly effective in relieving pain from renal colic, but their role in treating biliary colic is not established. A preliminary study showed that intramuscular (IM) diclofenac sodium (Voltaren) provided more symptomatic relief than either placebo or papaverine, while decreasing the likelihood of progression to acute cholecystitis. However, that study had design flaws, such as inadequate blinding and a follow-up period of only 24 hours.[1] The current study attempted to confirm these findings using a more rigorous design and longer follow-up.

Population studied Patients presenting to the emergency room of a general hospital in Greece with right upper quadrant or epigastric pain who had ultrasonographic evidence of gallstones were considered. Exclusion criteria included a dilated common bile duct, mild pain, fever, jaundice, signs of peritoneal irritation, microscopic hematuria, increased urine amylase, analgesic or antibiotic use within the prior 8 hours, and a history of peptic ulcer disease. Of the 53 patients enrolled, the mean age was 58 years and 72% were female.

Study design and validity Patients were randomized to receive a single injection of 75 mg of IM diclofenac sodium or an equivalent volume of saline. Both patients and investigators were blinded. All patients were admitted to the hospital for a minimum of 72 hours. The two groups were very similar with regard to age, sex, baseline clinical characteristics, and the average duration of pain at presentation (17 hours). The same clinician evaluated each patient every 15 minutes for the first 2 hours, every 60 minutes for the next 6 hours, and every 12 hours thereafter (or sooner for complaints of pain). Patients whose pain either did not improve within 2 hours of the initial injection or recurred were given 75 mg of IM propoxyphene hydrochloride every 6 hours as needed. Only one patient dropped out of each group, and data were appropriately analyzed on an intention-to-treat basis.

Outcomes measured There were two primary endpoints: the initial pain response to treatment (no improvement, improvement, or total relief), and the development of complications (acute cholecystitis, obstructive jaundice, cholangitis, or pancreatitis). Secondary endpoints included time to pain relief, recurrence of pain, time to recurrence of pain, and total propoxyphene use during the first 72 hours.

Results Patients receiving diclofenac were significantly more likely to have complete relief of pain than those receiving placebo (21/27 vs 7/26; $P = .0003$). Two patients have to be treated with diclofenac for one to benefit (NNT = 2). A similar number in each group had recurrence of pain (10 given diclofenac vs 8 given placebo), but the time to recurrence was longer in the diclofenac group (18.9 vs 7.2 hours; $P = .018$). Eleven of the diclofenac patients required propoxyphene (mean dose 64 mg) vs 17 of the placebo patients (mean dose 114 mg); these differences were not significant. Regarding complications, 4 patients in the diclofenac group developed acute cholecystitis vs 11 in the placebo group ($P = .04$; absolute risk reduction [ARR] = 27% ; NNT = 3.7). Similar numbers of patients in each group developed obstructive jaundice, cholangitis, or pancreatitis (9 in diclofenac group vs 10 in placebo group). Overall, 13 patients underwent cholecystectomy during the hospitalization: 2 for acute cholecystitis (one patient from each group) and 11 electively. Adverse reactions to diclofenac were not observed in any patient.

Recommendations for clinical practice **This well-designed study corroborates the effectiveness of a single 75-mg IM injection of diclofenac in relieving pain from biliary colic and preventing short-term complications. However, because the average duration of pain on presentation in this study was longer than the usual 1 to 5 hours associated with uncomplicated biliary colic and the number of patients who developed complications was higher than would be expected,[2] it is possible**

that some patients actually had acute cholecystitis at enrollment. It is not known whether diclofenac, or any other NSAID, is more effective than parenteral narcotics, the traditional treatment for biliary colic; a direct comparison would be beneficial.

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Calcium Does Not Prevent Preeclampsia

Reference Levine RJ, Hauth JC, Curet LB, et al. Trial of calcium to prevent preeclampsia. N Engl J Med 1997; 337:69-76.

Clinical question **Does daily supplementation with 2 g of calcium reduce the incidence or severity of preeclampsia in healthy nulliparous women?**

Background Previous trials, including several meta-analyses, have suggested that calcium supplementation during pregnancy may reduce the risk of preeclampsia. Questions regarding the validity of individual study designs and the low dietary calcium intake in some study populations have limited the acceptance of past trials.

Population studied The study population included 4589 nulliparous, healthy pregnant women selected from an initial pool of 11,959. The racial breakdown was 35% white non-Hispanic, 17% white Hispanic, 45% black (including black Hispanic), and 2% other. Exclusion criteria included evidence of renal disease, hematuria, or a history of urolithiasis in the patient or a first-degree relative.

Study design and validity Eligible women were initially screened using a single-blind compliance test and then randomly assigned in a double-blind fashion to receive either blister-packed calcium carbonate supplement (2 g daily) or placebo. Blister packs were collected at each office visit to determine compliance. All subjects began using the blister packs before their 22nd week of gestation and were seen every 4 weeks through the 29th week, every 2 weeks through the 35th week, and weekly thereafter.

The strength of this study rests on the large number of subjects involved and the care that was taken to determine the rate of compliance within each group. Only 253 women were lost to follow-up, including 132 in the calcium group and 121 in the placebo group. Data analysis was by intention to treat.

Outcomes measured The primary outcome measured was preeclampsia, defined as pregnancy-associated hypertension and proteinuria occurring within 7 days of each other. Hypertension was defined as a diastolic blood pressure of 90 mm Hg or greater on two occasions 4 to 168 hours apart. Secondary maternal outcomes measured included urolithiasis, severe preeclampsia, eclampsia, and the HELLP (hemolysis, elevated liver enzymes, and low platelet counts) syndrome. Perinatal outcomes monitored included gestational age at delivery, birthweight, Apgar scores, perinatal mortality, and neonatal hypocalcemia.

Results The incidence of preeclampsia was 6.9% in the calcium group and 7.3% in the placebo group (nonsignificant relative risk, 0.94; 95% CI, 0.76 to 1.16). There was no statistically significant difference between the groups in the incidence of severe preeclampsia, eclampsia, the HELLP syndrome, and pregnancy-associated hypertension without preeclampsia. Group differences between the mean systolic and diastolic blood pressures were less than 1 mm Hg. There were no significant differences between the groups in other important obstetrical or perinatal outcomes. There were also no increases in maternal urolithiasis or neonatal hypocalcemia in the calcium-treated group. Subgroup analyses did not show treatment differences related to maternal age or baseline dietary calcium intake.

Recommendations for clinical practice **This large, well-designed, and rigorously conducted trial provides conclusive evidence that the use of calcium supplementation does not prevent preeclampsia in healthy nulliparous women, including adolescents and women with poor dietary intake of calcium. This study does not address the question of whether calcium supplementation can prevent preeclampsia in women at increased risk, such as those with prior preeclampsia or chronic hypertension.**

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Carvedilol Following AMI

Reference Basu S, Senior R, Raval U, van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction: a placebo-controlled, randomized trial. Circulation 1997; 96:183-91.

Clinical question **Does treatment with carvedilol reduce the risk of subsequent cardiac events in patients with acute myocardial infarction?**

Background Although beta-blocker use after acute myocardial infarction (AMI) reduces the risk of mortality and cardiovascular events, these agents may cause or aggravate heart failure because of their negative inotropic effects. Their role in patients who receive thrombolytic therapy is also less well established. This study evaluated the effects of short- and long-term treatment with carvedilol (a new, nonselective beta-blocker with alpha-blocking properties) for patients with AMI.

Population studied Subjects included British patients admitted to a single coronary care unit within 24 hours following an acute myocardial infarction, including patients with acute heart failure. Patients were excluded if they were taking or had contraindications to alpha- or beta-blockers (other than heart failure), took calcium channel blockers, were in Killip class IV heart failure or cardiogenic shock, had severe bradycardia, hypotension, second- or third-degree heart block, left bundle branch block, severe valvular disease, insulin-dependent diabetes, renal failure, malignancy, other severe disease, or were pregnant.

Study design and validity In this double-blind, placebo-controlled trial, study subjects initially received placebo (n=74) or carvedilol 2.5 mg (n=77) intravenously started within 24 hours after admission. This dose was followed in 4 hours by oral placebo or carvedilol 6.25 mg. The dose was titrated to 12.5–25 mg orally twice daily and continued for 6 months. Diuretics for hypertension and nitrates for angina were allowed. Subjects were withdrawn from the study following a serious cardiovascular (CV) event.

Patients eligible for this study were evenly allocated to placebo or carvedilol based on infarct location and the use of thrombolytic agent. This stratification increases our confidence in the results, although most patients received a thrombolytic. Results were analyzed on an intention-to-treat basis and therefore includes patients with a serious CV event. However, differences between carvedilol and placebo may not be apparent because of the small number of patients included in this study.

Outcomes measured The primary outcome was the development of serious CV endpoints, including reinfarction, stroke, heart failure, and cardiovascular-related death. Secondary outcomes included the incidence of adverse drug effects and impact on hemodynamic measures and exercise tolerance.

Results Of the 416 patients eligible for this study, 265 (64%) were excluded. Thrombolytic therapy was used in 95% of subjects. Fewer serious CV events (n=18) occurred in the carvedilol group compared with placebo (n=31, P<.02). Benefits occurred as early as 1 week and continued for the complete 6 months of the trial. Other variables, including ejection fraction, were not affected by long-term therapy. Although overall adverse event rates were similar in each group, dizziness was more common in the carvedilol group (6.5% vs 1.4%). No subject withdrew because of dizziness.

In the 54 patients with clinical evidence of acute heart failure at enrollment, the incidence of cardiac events was similar whether carvedilol (38%) or placebo (45%) was given. At the end of 6 months, serious cardiac events in the group of patients with LVEF <45% were fewer in the carvedilol group compared with placebo (5 vs 14, P=.04).

Recommendations for clinical practice **Despite recent approval of carvedilol for the treatment of patients with chronic stable heart failure, this study does not provide enough evidence to advocate its use following an acute MI. The intravenous form of carvedilol used in this study currently is unavailable in the United States. Additionally, the extensive exclusions limit generalization of the results to family practice patients. Most patients presenting with AMI have concomitant illnesses that would preclude the use of carvedilol. Finally, the number of patients was not large enough to detect differences in the incidence of clinically important CV events such as reinfarction and unstable angina.**

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Inhaled Corticosteroids and Cataracts

Reference Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med 1997; 337:8-14.

Clinical question **Is there an increased risk of cataract formation with the use of inhaled corticosteroids?**

Background Cataracts can substantially affect a patient's sense of well-being and activities of daily living. Approximately 20% of people aged 65 to 75 have cataracts, increasing to 50% of people over 75. Along with age, ultraviolet-B radiation, diabetes mellitus, alcohol, certain drugs, and smoking have been identified as possible risk factors for the development of cataracts. Oral corticosteroid use is clearly associated with posterior subcapsular cataracts (PSC), a subtype that tends to more severely affect vision. While previous epidemiologic studies have not found an association with inhaled

corticosteroids, these studies were conducted on children, a group with a very low rate of cataract formation.

Population studied The Blue Mountains Eye Study is a population-based study in an urban area west of Sydney, Australia. Everyone in the region over the age of 50 was asked to enroll. The 3654 subjects represented a 82% enrollment rate. Beclomethasone was the primary inhaled corticosteroid used in Australia during the study period.

Study design and validity This is a cross-sectional, population-based study that collected patient-reported medication use and medical history. Subjects' lenses were photographed, and these photographs were graded for type, size, and severity of cataract. This study is limited by the use of patient recall to estimate medication use, missing data, and probable confounding. The cumulative lifetime dose of inhaled corticosteroids was estimated from the length of use and average daily dose. The photographs from 29% of subjects were unusable because of a camera problem. However, possible confounding variables were grouped simplistically; for example, smoking history was reported as current smoker, past smoker, or never smoked. Given the likely interaction between smoking and the disease processes for which inhaled corticosteroids are used (asthma, chronic obstructive pulmonary disease), confounding by smoking exposure remains a possibility.

Outcomes measured The primary outcome was the age and sex-adjusted prevalence ratio for the presence of cataracts. In addition, multivariate analysis was used to adjust for possible confounders, such as sun-related skin damage, diabetes, hypertension, and tobacco use.

Results The age and sex-adjusted relative prevalence ratio was 2.6 (95% CI 1.7 to 4.0) for the presence of PSCs in patients who are current users of inhaled corticosteroids. For those with over 2 g total dosage of beclomethasone (almost 7 years at 8 puffs per day), the prevalence ratio was 5.5 (95% CI 2.3 to 13.0). Having ever used inhaled corticosteroids increased the relative prevalence ratio to 1.5 (95% CI 1.2 to 1.9) for nuclear cataracts and to 1.9 (95% CI 1.3 to 2.8) for PSCs. Multivariate analysis did not significantly change these results.

Recommendations for clinical practice **This study raises the possibility that inhaled corticosteroids are associated with the presence of cataracts. The connection is biologically plausible, since oral corticosteroids are clearly linked to PSCs and inhaled corticosteroids are known to be absorbed systemically. In addition, there appears to be a dose-response relationship. Although limited, this study is the best evidence to date of a possible connection. However, there is clear therapeutic advantage to the use of these medications, and this study should not cause physicians to significantly decrease their use in patients who are benefiting from them. Clinicians should be aware of the possible association between cataracts and the use of inhaled corticosteroids, particularly among patients who are using higher doses for longer periods, and should inform and monitor patients accordingly.**

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Epidural Injections for Sciatica

Reference Carette S, Leclaire A, Marcoux S, et al. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. N Engl J Med 1997; 336:1634-40.

Clinical question **Are epidural corticosteroid injections helpful in patients with sciatica due to herniated nucleus pulposus?**

Background If conservative measures fail, an important option for primary care providers is referral for epidural corticosteroid injections. However, the evidence supporting injections is weak: only half of the 12 controlled trials have found injections to be efficacious, and most of these trials had methodologic deficiencies. This study used rigorous methodology to evaluate the efficacy of epidural corticosteroid injection.

Population studied This study enrolled 158 adults with a first or recurrent episode of sciatica (constant or intermittent pain in one or both legs, radiating below the knee) lasting 4 weeks to 1 year. All patients had corresponding CT evidence of a herniated nucleus pulposus. Patients were excluded if there was CT evidence of nerve root compression from causes other than a herniated nucleus pulposus, symptoms or clinical findings consistent with cauda equina syndrome, if they had received corticosteroid injections for the current episode in the preceding year, or if they had undergone low back surgery. Subjects were referred from both primary care physicians and specialists; prior treatment of patients is not described, but the median duration of the current episode of pain was approximately 13 weeks. In general, the subjects seem similar to those of primary care providers who have received initial conservative management.

Study design and validity This was a random-

ized, double-blind, placebo-controlled trial. The subjects were injected weekly with either methylprednisolone acetate (80 mg in 8 mL) or normal saline (1 mL) up to 3 times and reevaluated at 3, 6, and 12 weeks. Physicians and nurses assessing outcomes were blinded to study group, and follow-up was excellent (over 98%). Analysis was by intention to treat, with adjustment of baseline differences by analysis of covariance; there was no correction for multiple comparisons. While the choice of placebo is not perfect (the smaller volume of injection may have reduced the impact of the placebo), the overall study design is strong.

Outcomes measured The primary outcome was functional status at 3 months, as measured by the Oswestry Low Back Pain Disability Questionnaire, a well-known and valid scale. Secondary outcomes included other measures of functional status (Sickness Impact Profile and patient report of limitation of activities), patient reported pain intensity and rating (from the McGill Pain questionnaire), physician examination of sensation and the extent of forward flexion, medication use, and 12-month cumulative probability of back surgery. From the perspective of the referring physician, these are the key outcomes. Ideally, cost and patient satisfaction with care should also have been assessed.

Results The two groups were similar at baseline except that the corticosteroid group had more men and more patients living with a partner. These differences were adjusted for statistically and did not affect the overall results. In general, both corticosteroid and placebo groups had moderately improved functional status over the trial. At 3 weeks, the corticosteroid group had greater improvement in forward flexion and fewer sensory deficits, but these differences disappeared rapidly. At 3 months, there was no significant difference between the two groups in any of the outcomes, and about 25% of patients in each group underwent surgery in the 12 months after randomization. The dura was accidentally punctured in one patient in each group, requiring a blood patch, and 37 of the subjects reported a transient headache within 24 hours of at least one injection.

Recommendations for clinical practice **This report provides good evidence that epidural corticosteroid injections provide little long-term improvement of functional status, self-reported pain intensity or quality, and the rate of surgery for unselected patients with sciatica due to a herniated disk. As has been shown for many other interventions, it has been very difficult to improve on the natural history of low back pain—even, as in this case, when it is subacute. Future research should attempt to identify subtypes of low back pain that might respond to specific therapy or explore the effectiveness of a chronic disease model in managing these patients.**

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Safety of Newborn Early Discharge

Reference Liu LL, Clemens CJ, Shay DK, Davis RL, Novack AH. The safety of newborn early discharge: the Washington State experience. JAMA 1997:278:293-8.

Clinical question **How soon can normal newborns be safely discharged from the hospital?**

Background The length of hospital stay for healthy newborns and their mothers has been decreasing steadily over the last 15 years because of cost-containment on the part of insurers and because of patient demand. Recent federal legislation requires insurers to cover a 48-hour stay postpartum. Studies to date have not given clear results to help policymakers and physicians address the safety of this issue.

Population studied Case subjects included all infants born in Washington State from 1991 to 1994 who were readmitted to the hospital within the first 28 days of life. Exclusion criteria included less than 36 weeks' gestation, multiple births, cesarean section births, and infants with meconium aspiration syndrome, pneumonia, and serious birth defects. Newborns whose length of stay could not be estimated were also excluded, leaving 2029 "normal" infants in the case population. Four control infants were matched to each case by year of birth from the same population of healthy infants who were not rehospitalized within 28 days. The maternal population was predominately white with few teen pregnancies.

Study design and validity This was a case-control study comparing exposure to a specific risk factor (hospital discharge at <30 hours of age) and whether infants experienced hospital readmission within 28 days of birth. Information was extracted from a statewide database linking birth and death certificate data with maternal and infant hospital admission and discharge records. Specific data on outpatient services received after discharge such as visiting home nurses were not available. These services were uncommon during the study period.

Case-control studies are useful for finding association but weaker in proving causation, as the data are ret-

rospective and there is a greater likelihood for unknown confounding variables and bias. However, a prospective randomized trial of early hospital discharge is unlikely to be performed because of the ethical constraints of randomization and the large number of subjects needed.

Outcomes measured The primary outcome measured was risk of readmission within 28 days for infants discharged less than 30 hours after birth, compared with those discharged between 30 and 78 hours after birth. Secondary outcomes measured included the risk of hospitalization at 7 and 14 days and the risk for subpopulations of infants including those with mothers who were primiparas, less than 18 years of age, had Medicaid coverage, lived in rural areas, who had high school education or less, or who were unmarried. The risk of readmission for infants with specific diagnoses such as jaundice, dehydration, and sepsis was also analyzed.

Results Only 2% of all newborns developed subsequent problems severe enough to warrant rehospitalization in the first month of life. Healthy newborns discharged at less than 30 hours of age were more likely to be rehospitalized at 7, 14, and 28 days after discharge than infants with longer initial hospital stays. This risk was greatest in the first 7 days after discharge. Interestingly, the subgroup of infants discharged on their date of birth did not experience an increased risk of rehospitalization. Subgroups at increased risk for rehospitalization following early discharge included newborns born to primigravidas, mothers younger than 18 years, and mothers with premature rupture of membranes. Early discharge was associated with an increased risk of readmission for jaundice. Increased risks were also found for dehydration and sepsis, though the differences were not statistically significant. Among healthy newborns with no other diagnosis, 8 of every 100 hospitalizations in the first 28 days of life could be preventable if the infants were discharged after 30 hours of age.

Another article in the same journal looked at a similar cohort of newborns during the same study period.[1] Readmission to the hospital for feeding difficulties was not associated with early discharge. The sample size of this trial was smaller than the former and may have lacked sufficient power for detecting a true difference in readmission rates.

Recommendations for clinical practice **Early newborn discharge less than 30 hours after birth increases the risk of rehospitalization. Reducing this risk, however, will likely require keeping newborns in the hospital for at least 3 to 4 days. It remains uncertain whether this strategy would be cost-effective. Evidence regarding the effect of high-quality follow-up after discharge on readmission rates is lacking. Family physicians should continue to individualize care and encourage the establishment and use of high-quality post-discharge monitoring of the mother and infant.**

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Omeprazole Maintenance Therapy for GERD

Reference Venables TL, Newland RD, Patel AC, Hole J, Copeman MB, Turbitt ML. Maintenance treatment for gastro-oesophageal reflux disease. A placebo-controlled evaluation of 10 milligrams omeprazole once daily in general practice. Scand J Gastroenterol 1997; 32:627-32.

Clinical question **Is omeprazole 10 mg once daily effective for maintenance treatment of GERD?**

Background Without maintenance treatment, patients with healed reflux esophagitis confirmed by endoscopy will have relapse rates of 86% by endoscopic criteria and 66% by symptomatic criteria within a 12-month period.[1] The current study analyzed the efficacy of omeprazole 10 mg once daily vs placebo for maintenance treatment.

Population studied Adults aged 18 years and older with symptoms of heartburn for 3 months or more underwent endoscopy. Patients were eligible for study inclusion if endoscopy revealed nonerosive esophagitis. Patients were excluded if they used an antisecretory drug within the previous month or if they had erosive esophagitis, peptic/duodenal ulcer, Barrett's esophagitis, or complicating symptoms such as melena or hematemesis.

Study design and validity After endoscopic evaluation, all patients were treated initially for gastroesophageal reflux disease (GERD) with omeprazole 10 mg once daily, omeprazole 20 mg daily, or ranitidine 150 mg twice daily for 4 weeks. Patients with persistent symptoms received an additional 4 weeks of omeprazole 20 mg daily. The authors did not say if the patients were randomized during this initial treatment phase. After this phase of the study, 495 patients were randomized to maintenance treatment with either omeprazole 10 mg or placebo once daily. Investigators and patients were unaware of treatment assignment. Patients were also given a supply of antacids to use as needed. Patients were assessed at 8-week intervals for 6 months.

This study was a double-blind, placebo-controlled trial with a large sample size. The study outcomes

are based on symptomatic relapse, which is what is most valuable to the family physician. The authors did not randomize the initial acute treatment groups, which may ultimately influence relapse rates. Likewise, the amount of antacids that patients used was not quantified.

Outcomes measured Heartburn symptoms were graded by self-report of severity and frequency, and patients completed the Gastrointestinal Subjective Rating Scale at each visit. Quality of life was measured using the Psychological General Well-Being Index.

Results During the 6-month study period, 49% of patients in the placebo group and 20% of patients in the omeprazole group relapsed. General well-being was not affected by therapy, though reflux syndrome scores were significantly better in the omeprazole group. At 16 weeks, heartburn symptoms were still experienced by 56% of the placebo group and 37% of the omeprazole group ($P<.001$). Adverse events were equal between the two groups. Overall, 80% of patients in the omeprazole group were asymptomatic after 6 months.

Recommendations for clinical practice **Although not all patients with GERD require maintenance treatment, it is necessary for patients with erosive esophagitis, residual symptoms after initial treatment, or prolonged initial therapy.[2] Safety of long-term use of the proton pump inhibitors was once an issue of debate. However, studies of omeprazole use for up to 5 years have shown no increased incidence of carcinoma.[3] This study shows that omeprazole 10 mg once daily is effective maintenance treatment for GERD based on symptom control.**

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"Statin" Drugs, Mortality, and Stroke Prevention

Reference Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. JAMA 1997; 278: 313-21.

Clinical question **Do "statin" drugs for lowering cholesterol prevent stroke or decrease mortality?**

Background Elevated cholesterol is a known risk factor for coronary heart disease (CHD) but not for stroke. Treatment of high cholesterol with HMG Co-A reductase inhibitors (statins) reduces morbidity from heart disease in both primary and secondary prevention trials. No single trial has found a benefit for stroke prevention, and only one has found a statistically significant reduction in overall mortality. A smaller meta-analysis looking only at stroke prevention was published 1 month prior to the Hebert et al study; although different methods of combining and analyzing data were used,[1] its results were consistent with the Hebert et al study.

Population studied Participants in all 16 published randomized controlled trials of a statin drug as monotherapy were included. Subjects in these trials were men and women from several European countries, the United States, and Canada, including both asymptomatic people (primary prevention) and those with known CHD (secondary prevention) and people with average as well as elevated cholesterol. Sixteen of the trials included total mortality as an outcome and 14 reported information about stroke as an outcome. Follow-up ranged from 8 weeks to 5.4 years.

Study design and validity This is a meta-analysis that statistically combines the results of all previously published randomized controlled trials. To date, most individual trials have not found an effect on stroke or overall mortality. By combining the results of these trials into one large meta-analysis, the authors correct for the possibility of inadequate sample size in the individual studies. Since statins have been proven to decrease CHD in patients with hypercholesterolemia, it would probably be unethical to carry out a new study large enough to demonstrate an effect of statins on stroke prevention. Thus, meta-analysis is the most appropriate design to answer these clinical questions. The authors provide detailed information on their statistical calculations and methods, which appear appropriate. One minor limitation is that the authors did not search the foreign language literature. All data were analyzed using the intention-to-treat approach.

Outcomes measured The two primary outcomes studied were total mortality and stroke. Secondary analyses looked at fatal vs nonfatal stroke, all cardiovascular deaths, CHD, fatal CHD, and cancer deaths. Odds ratios with confidence intervals were used as the measure of effect.

Results There were 29,008 total subjects in the 16 trials. The authors found a 22% reduction in total mortality and a 29% reduction in stroke among subjects randomized to a statin drug compared with those ran-

domized to placebo. There was no statistically significant reduction in fatal stroke. Strokes were significantly prevented only in those with known heart disease. There was no increase in cancer deaths. The authors do not present number needed to treat (NNT) as a measure of effect. My calculations based on the crude numbers show that one must treat 106 people without CHD or 34 people with previously known CHD to prevent one death. One stroke can be prevented by treating 96 people, and one myocardial infarct (MI) by treating 28 people.

Recommendations for clinical practice **Statin drugs are effective in preventing death, coronary heart disease, and stroke. This has not been consistently demonstrated for any other class of cholesterol-lowering medications. Thus, statin drugs are clearly the treatment of choice for hypercholesterolemia. The risk reduction is greater for patients with higher baseline cholesterol values. When to treat and whether to treat a given patient depends on many factors including the patient's baseline cholesterol, other risk factors for vascular disease, and personal health beliefs. For comparison purposes, the effectiveness demonstrated in this trial compares favorably with treatment of mild hypertension (700 needed to treat to prevent one MI, stroke, or death) but not as favorably with treatment of severe hypertension (15 needed to treat to prevent one MI, stroke, or death).**

The data are strongest for pravastatin for primary prevention and simvastatin for secondary prevention. However, I believe it is appropriate to extrapolate these results to all drugs of this class. One note of caution: the follow-up in all of these studies was fairly brief, and the medications themselves are new. Clinicians should pay attention to follow-up studies evaluating the safety of long-term use of statin.

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