# Diuretics are first choice for hypertension

*Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003; 289:2534–2544.*

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## PRACTICE RECOMMENDATIONS

Low-dose diuretics are equal or superior to all other major classes of antihypertensive medications in improving long-term cardiovascular outcomes. Given that diuretics are also inexpensive and have a favorable side-effect profile, clinicians should use low-dose diuretics (eg, hydrochlorothiazide 25 mg/d or less) as a first choice for almost all patients with hypertension.

Clinicians should keep in mind that many patients require more than 1 medication. They should look for further information from pooled studies regarding specific populations such as those with diabetes or chronic renal disease, the elderly, or persons of color.

## BACKGROUND

Hypertension is common in family practice, but controversy remains about which medication should be used first. This network meta-analysis compares the efficacy of 6 common classes of antihypertensive agents: diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and alpha-blockers.

## POPULATION STUDIED

This study identified 42 trials with 192,478 patients in many countries, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study and the Australian National Blood Pressure Study. Some studies included patients with renal disease, diabetes, or existing cardiovascular disease, but those recruiting patients with congestive heart failure or prior myocardial infarction were excluded.

No information about age, gender, race, or medical comorbidities was given. Results are likely to be applicable to a typical family practice, but more information about important subgroups, such as the elderly or African Americans, would be valuable.

## STUDY DESIGN AND VALIDITY

Network meta-analysis is a novel methodology that combines direct evaluation of a treatment through traditional meta-analysis with indirect evaluation through comparing effects across trials that share a third treatment in common. Thus, if trial X compares treatments A and B, and trial Y compares treatments B and C, an indirect approach allows comparison of A and C. A network approach is very appropriate for studies of antihypertensives, which represent a patchwork of clinical trials for many different agents.

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## What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Practice Recommendation and summarizes the study's objective, patient population, study design and validity, and results. The collected POEMs are available online at www.jfponline.com.

The authors used MEDLINE, journal reviews, and previous meta-analyses to identify all randomized trials of antihypertensive therapy that evaluated major cardiovascular disease endpoints after at least 1 year. Trials with nonfactorial multiple risk interventions or that used agents other than those noted above were excluded.

Diuretic arms are divided into low-dose (12.5–25 mg) or high-dose (≥50 mg) administration of hydrochlorothiazide, chlorthalidone, or equivalent. Data were abstracted independently by 2 individuals, and were pooled to generate a total estimate of effect based on both direct and indirect estimates. Statistical coherence, a measure of heterogeneity in both direct and indirect measures, was also assessed.

The methodology was good. The strengths were the comprehensive search and the large number of trials with corresponding precision of pooled estimates; weaknesses included lack of blinding in search and data extraction, lack of correction for multiple comparisons, and lack of attention to possible confounding factors such as study quality, specific comorbidities, age, and race.

### OUTCOMES MEASURED

The primary outcomes measured were coronary heart disease events, congestive heart failure, stroke, total cardiovascular events, cardiovascular mortality, and total mortality. Side effects, cost, quality of life, and patient satisfaction were not addressed.

### RESULTS

Low levels of incoherence were present for all comparisons. Diuretics decreased all measured outcomes, including cardiovascular disease events (relative risk [RR]= 0.79; 95% confidence interval [CI], 0.69–0.92), congestive heart failure (RR=0.51; 95% CI, 0.42–0.62), stroke (RR=0.71; 95% CI, 0.63–0.81), and total mortality (RR=0.90; 95% CI, 0.84–0.96).

Compared with calcium-channel blockers, low-dose diuretics lowered risks of congestive heart failure (direct RR=0.50; 95% CI, 0.27–0.92; indirect RR=0.85; 95% CI, 0.68–1.05). Compared with ACE inhibitors, low-dose diuretics were associated with reduced risks of congestive heart failure (RR=0.88; 95% CI, 0.80–0.96), cardiovascular events (RR=0.94; 95% CI, 0.80–0.98), and stroke (RR=0.86; 95% CI, 0.77–0.97).

Diuretics decreased all measured outcomes, including cardiovascular disease, stroke, and total mortality

Compared with beta-blockers, low-dose diuretics were associated with a reduced risk of cardiovascular events (RR=0.89, 95% CI, 0.80–0.98). Compared with alpha-blockers, low-dose diuretics were associated with reduced risks of congestive heart failure (RR=0.51; 95% CI, 0.43–0.60) and cardiovascular events (RR=0.84; 95% CI, 0.75–0.93). There are relatively few trials for alpha-blockers and ARBs.

No significant differences were seen in blood pressure changes among the medications.

## Many abnormal PSA test results normalize over time

*Eastham JA, Riedel E, Scardino PT, et al. Variation of serum prostate-specific antigen levels. An evaluation of year-to-year fluctuations. JAMA 2003; 289:2695–2700.*

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### PRACTICE RECOMMENDATIONS

A significant proportion of prostate-specific antigen (PSA) tests with abnormal results—nearly half—normalize over 1 to 4 years of follow-up without any medical or surgical intervention. This information can be used by physicians and their patients in shared decision-making about both PSA screening and in deciding how to follow up an abnormal result.

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## Nearly half of all abnormal PSA test results will normalize within 1 to 4 years without treatment

### BACKGROUND

PSA is frequently used for prostate cancer screening. Positive screening values often lead to biopsy and other invasive interventions, but the long-term natural history of PSA levels is not known.

### POPULATION STUDIED

The researchers studied PSA levels of men previously enrolled in a dietary intervention trial to reduce the recurrence of colon polyps (Polyp Prevention Trial, 1991–1998). The trial included men aged >35 years having a colon adenomatous polyp removed within 6 months of the trial.

The researchers excluded men with familial adenomatous polyposis or premature colon polyps (<35 years), invasive large bowel cancers, or inflammatory bowel disease. They also excluded men with prior prostate cancer and those not completing all yearly blood samples.

Of 1351 men in the original trial, 972 were included in this report. Approximately one third were aged <60 years, one third were aged 60–69 years, and one third were aged >70 years (only 1 was >80 years).

### STUDY DESIGN AND VALIDITY

This is a descriptive, 4-year longitudinal cohort from a randomized controlled trial conducted between 1991 and 1998. The researchers analyzed PSA results from frozen blood samples collected in the original trial at baseline and at four 1-year intervals. Previous work demonstrated acceptable long-term stability of frozen total PSA.

The researchers excluded 26 subjects from a portion of their analysis due to prostate cancer development during the study period (23 documented and 3 highly suspicious PSA trajectories). This was appropriate given the paper's focus on natural history.

A simple sensitivity analysis of the scenario most likely to bias the reported observations is thus appropriate. Using a scenario in which it is assumed that:

- all 26 men with prostate cancer had PSA levels in the abnormal range for all criteria
- at least 2 blood draws remained after the abnormal result
- the PSA levels would never normalize

then alternative results, using this scenario, are presented in brackets after the values found in the original analysis. This secondary analysis does not reflect any predictive values of the PSA itself, but rather reframes the study observations to more accurately reflect real-world results.

### OUTCOMES MEASURED

The study measured PSA levels (ng/mL) at the following clinical standards: total PSA >2.5, total PSA >4.0, age-specific total PSA levels, free/total PSA <0.25, or PSA velocity >0.75.

### RESULTS

For the criterion of total PSA >2.5, 37% of men had at least 1 positive value. Among the 291 [317] men with an abnormal value and at least 1 remaining blood draw, 40% [36%] had values return to the normal range on at least 1 subsequent occasion. For 62 [88] men who had at least 2 subsequent blood draws remaining, 65% [45%] had 2 consecutive normal levels.

For the criterion of total PSA >4.5, 21% of men had at least 1 positive value. Among the 154 [180] men with an abnormal value and at least 1 remaining blood draw, 44% [37%] had values return to the normal range on at least 1 subsequent occasion. For 40 [66] men who had at least 2 subsequent blood draws remaining, 80% [48%] had 2 consecutive normal levels.

For the age-specific PSA criteria, 18% of men had at least 1 positive value. Among the 117 [143] men with an abnormal value and at least 1 remaining blood draw, 55% [44%] had values return to the normal range on at least 1 subsequent occasion. For 35 [61] men who had at least 2 subsequent blood draws remaining, 83%

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[47%] had 2 consecutive normal levels.

For the free-total PSA criterion, 20% of men had at least 1 positive value. Among the 143 [169] men with an abnormal value and at least 1 remaining blood draw, 53% [45%] had values return to the normal range on at least 1 subsequent occasion. For 43 [69] men who had at least 2 subsequent blood draws remaining, 74% [46%] had 2 consecutive normal levels.

## Ezetimibe plus atorvastatin lowers cholesterol

*Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; 107:2409–2415.*

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### PRACTICE RECOMMENDATIONS

Ezetimibe plus atorvastatin lowers low-density lipoprotein (LDL) cholesterol more than either alone. When combined with low-dose atorvastatin (10 mg), ezetimibe achieves reductions similar to those seen with atorvastatin (80 mg) alone in LDL cholesterol, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, and triglycerides.

Despite these modest reductions in cholesterol, this study does not provide evidence that this combination lessens cardiovascular morbidity or mortality. With this caveat, adding ezetimibe to atorvastatin may be a reasonable alternative for patients already on high-dose atorvastatin who either can't reach target cholesterol levels or experience significant side effects.

### BACKGROUND

Ezetimibe is a new medication that prevents intestinal absorption of cholesterol. This trial assessed reductions in LDL cholesterol levels from coadministration of ezetimibe and atorva-statin compared with those of each drug alone.

### POPULATION STUDIED

The researchers conducting this trial enrolled 628 (primarily white) individuals aged ≥18 years with hypercholesterolemia (calculated LDL 145–250 mg/dL) and triglycerides ≤350 mg/dL.

Exclusion criteria included but were not limited to congestive heart failure; uncontrolled arrhythmias; recent myocardial infarction, coronary bypass surgery, or angioplasty; unstable or severe peripheral artery disease; unstable angina; uncontrolled or new diabetes; and renal dysfunction.

Across the treatment groups, the mean age was 56.7 to 58.7 years; 52% to 62% were female. Less than 10% had diabetes or coronary heart disease, and approximately 15% were current smokers. More than one third had hypertension and a family history of coronary heart disease.

### STUDY DESIGN AND VALIDITY

This industry-sponsored randomized, double-blind, placebo-controlled trial consisted of 3 phases. Screening included a 2- to 12-week washout of previous lipid-altering drug therapy and instruction in a National Cholesterol Education Program Step I (or stricter) diet.

Pre-randomization included a 4-week, single-blind, placebo-controlled lead-in with assessment of calculated LDL cholesterol samples to assure that no single value was <145 mg/dL or >250 mg/dL. The investigators then randomized patients to 10 treatment groups: placebo; ezetimibe 10 mg; atorvastatin 10, 20, 40, and 80 mg; and ezetimibe 10 mg plus atorvastatin 10, 20, 40, and 80 mg. They measured lipid profiles at baseline and at 2, 4, 8, and 12 weeks.

Strengths of the methodology include the randomized, double-blinded, controlled design and the use of intention-to-treat analysis. It is unclear whether allocation was concealed. The short, 12-week treatment period limits the assessment

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of rare and potentially serious side effects as well as long-term efficacy. The extensive exclusion criteria limit the generalizabilty of these results.

### OUTCOMES MEASURED

The investigators measured percent change in direct LDL cholesterol from baseline to final measurement. Secondary outcomes included change from baseline to final measurement of calculated LDL, total cholesterol, triglyceride, HDL cholesterol, and several other lipid-related variables. Patient-oriented outcomes, such as rates of death, stroke, or myocardial infarction were not addressed. Cost-effectiveness of the combination was not evaluated.

### RESULTS

Demographics and baseline characteristics were similar across treatment groups. Ninety-two percent of subjects completed the 12-week study. When the treatment groups were pooled together, the combination of ezetimibe with atorvastatin resulted in a greater mean decrease in direct LDL cholesterol than atorvastatin alone (–54.5% vs –42.4%; $P<.01$) or ezetimibe alone (–54.5% vs –18.4%; $P<.01$). This combination also resulted in statistically significant reductions in total cholesterol (–9%), triglycerides (–8%), and an increase in HDL cholesterol (3%) compared with atorvastatin alone.

When analyzed separately by dose, the combination of ezetimibe with atorvastatin 10 mg produced reductions similar to atorvastatin 80 mg alone for LDL (50% vs 51%), total cholesterol to HDL cholesterol ratio (43% vs 41%), and triglycerides (31% each). HDL levels were 6% greater at this combined dose (9% vs 3%).

Approximately 60% of patients in each group (including placebo) reported an adverse event. However, only 17% of patients treated with atorvastatin and 23% of patients receiving the combination therapy reported "treatment-related" adverse events. Events included mild to moderate gastrointestinal and musculoskeletal problems. One to two percent of patients receiving atorvastatin (alone or in combination) had a 3-fold rise in liver enzymes. Five percent of patients in each group discontinued treatment.

## Diet may slow progression of diabetic nephropathy

*Facchini FS, Saylor KL. A low-iron-available, polyphenol-enriched, carbohydrate-restricted diet to slow progression of diabetic nephropathy. Diabetes 2003; 52:1204–1209.*

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### PRACTICE RECOMMENDATIONS

A polyphenol-enriched diet with 50% carbohydrate restriction and low iron availability was superior to a conventional protein-restricted diet in slowing the progression of diabetic nephropathy.

These findings must be confirmed by additional high-quality studies before physicians can routinely recommend a change from the conventional low-protein diet. Current use of this diet is limited, as many nutritionists—even those specializing in diabetes—have no knowledge of it.

### BACKGROUND

Patients with end-stage renal disease are usually encouraged to follow a low-protein diet to slow the progression of their renal disease. This study was conducted to determine whether a carbohydrate-restricted, low-iron/polyphenol-enriched (CR-LIPE) diet was more effective than a conventional protein-restricted diet at slowing the progression of diabetic nephropathy. Foods rich in polyphenols include olive oil, green tea, cranberries, grapes, and red wine.

### POPULATION STUDIED

A total of 191 patients with type 2 diabetes—men and women aged 49 to 62 years who were

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referred to nephrology clinics in California for impending renal failure—were recruited. Subjects had a history of diabetes for 5 to 15 years, with glycosylated hemoglobin ($HbA_{1C}$) of 6.0% to 9.3%. Current medications for both hypertension management and glucose control were continued. When there was doubt as to the cause of renal failure, a renal biopsy was performed to confirm the diagnosis of diabetic nephropathy. The ethnicity of the subjects is not mentioned. Results are likely generalizable to a diabetic population with advanced renal disease seen in a nephrology clinic.

### STUDY DESIGN AND VALIDITY

This was a nonblinded, randomized controlled trial, although the method of randomization is not specified. Subjects were assigned with concealed allocation to either the CR-LIPE diet or the control diet, a conventional protein-restricted diet (0.8 g/kg). The main features of the CR-LIPE diet were 50% carbohydrate reduction; iron-enriched meats are replaced with iron-poor meats and foods known to inhibit iron absorption; elimination of all beverages apart from tea, water, and red wine; and the use of olive oil for frying and dressings. No attempt was made to assess compliance to either diet.

Analysis was by intention-to-treat; it is unknown whether the outcome assessors were blinded to group assignment. Patients were followed for a mean of 3.9 years (range, 0.7–5.3 years); 21 (11%) were lost to follow-up (9 in the CR-LIPE group, 12 in the control group). Weaknesses included small sample size, unclear method of randomization, lack of information on compliance with the diets, and uncertainty as to whether outcomes were assessed blindly.

### OUTCOMES MEASURED

Disease-oriented outcomes included doubling of serum creatinine and end-stage renal disease as defined by serum creatinine >6.0 mg/dL. Patient-oriented outcomes included the need for renal replacement therapy or transplantation and all-cause mortality.

### RESULTS

No significant difference was seen in the baseline characteristics of the 2 groups. Serum creatinine doubled in 19 (21%) of patients on the CR-LIPE diet vs 31 (39%) control subjects ($P<.01$). Renal replacement therapy or death occurred in 18 (20%) of patients on the CR-LIPE diet and in 31 (39%) control subjects ($P<.01$; number needed to treat=5).

These findings were independent of initial serum creatinine, 24-hour protein, blood pressure, $HbA_{1C}$, and the use of angiotensin-converting enzyme inhibitors.

## Naturopathic ear drops minimally effective for acute otitis media

*Sarrell EM, Cohen HA, Kahan E. Naturopathic treatment for ear pain in children. Pediatrics 2003; 111:e574–579.*

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### PRACTICE RECOMMENDATIONS

In children aged 5 to 18 years with acute otitis media, naturopathic herbal ear drops accounted for a small change in reported otalgia over 48 hours.

This study does not provide strong evidence for using naturopathic herbal ear drops in the studied population, let alone the population we most often see with otalgia due to acute otitis media: infants aged 6 to 24 months. Since no adverse events were reported, it seems reasonable to allow parents this option if they desire a nonpharmacologic analgesic—although the study does, once again, point out that time is often the best treatment for acute otitis media.

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## Time and not medication is often the best treatment for acute otitis media

### BACKGROUND

Given evidence suggesting that antibiotics provide little benefit for most children with acute otitis media, recent studies have focused on effective, safe analgesics to ease pain while awaiting spontaneous resolution. This study examined the effectiveness of naturopathic herbal ear drops for relieving otalgia as compared with traditional analgesics, with and without antibiotics.

### POPULATION STUDIED

The study enrolled 180 children in Israel aged 5 to 18 years who presented with ear pain and were found to have acute otitis media. Acute otitis media was diagnosed if middle-ear effusion was present (decreased mobility with pneumatic otoscopy or tympanogram, or visible bubbles or air-fluid level) with at least 1 other marker of inflammation (marked redness, distinct fullness, or bulging of the tympanic membrane).

The investigators excluded patients who had been treated with any ear drop or analgesic within 4 hours of the exam; children with otorrhea, ear drum rupture, or ventilation tubes; or complications of ear disease in the past 2 weeks.

### STUDY DESIGN AND VALIDITY

Subjects were randomly assigned to 1 of 4 groups. Group A received naturopathic herbal ear drops (abstracts of *Calendula officinalis* [marigold] flores, *Hypericum perforatum* [St. John's wort] herba tota, and *Verbascum thapsus* [mullein] flores in olive oil and the essential oils *Allium sativum* [garlic], *Lavandula officinalis* [lavender], and tocopherol acetate [vitamin E]), 5 drops 3 times daily. Group B received herbal ear drops with amoxicillin 80 mg/kg/d, divided into 3 doses. Group C received a topical anesthetic (amethocaine and phenazone) 5 drops 3 times daily. Group D received topical anesthetic with amoxicillin. Herbal ear drops and anesthetic drops were given at the time of diagnosis and then in the morning of 2 subsequent days.

This study had several weaknesses. Though the study was performed in children aged 5 to 18 years, the vast majority of acute otitis media occurs in children aged 6 to 24 months, and these results may not apply to younger children. The study was not truly double-blinded, as children were not given an oral placebo. This might lead to overestimating the effect of the drops in those receiving antibiotics, since this group may believe more strongly that they were improving.

The authors did not use an intention-to-treat analysis, as only 171 of 180 enrollees were analyzed; 9 children were removed from analysis after randomization due to noncompliance. Intention-to-treat analysis is important because it preserves the baseline comparability between groups at randomization, and more realistically reflects the performance of a given treatment in actual practice, where compliance is never 100%.

Pain was assessed with an unvalidated visual analog scale. The major finding of the study—that those given ear drops alone had statistically significantly greater pain relief than those receiving drops and antibiotics—was reported in the discussion; the actual results were not presented.

### OUTCOMES MEASURED

Ear pain was assessed using the Pain-O-Meter, a visual analog scale devised by the authors. Pain measurements were taken each day at the time drops were instilled, then 15 and 30 minutes later.

### RESULTS

Otalgia was reduced by 93% in the groups using naturopathic herbal ear drops with or without antibiotics, and 81% in the groups using anesthetic drops with or without antibiotics; the authors don't indicate whether this difference was statistically significant. Linear regression analysis showed that time alone accounted for 78% of the pain reduction, whereas naturopathic herbal ear drops accounted for 7.3% ($P$=.0001).

# Anticholinergics reduce symptoms of overactive bladder

*Herbison P, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared to placebo in the treatment of overactive bladder: systematic review. BMJ 2003; 326:841–847.*

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## PRACTICE RECOMMENDATIONS

Anticholinergic drugs such as tolterodine and oxybutynin produce a small effect on the symptoms of overactive bladder, decreasing slightly the number of episodes of leakage and the frequency of urination. The standard conservative intervention of bladder retraining has not been compared with anticholinergic drugs and their effect in combination has not been studied.

## BACKGROUND

Clinicians often use anticholinergic agents as the drugs of choice for overactive bladder. However, there is no consensus regarding the efficacy of these drugs in reducing the symptoms of overactive bladder.

## POPULATION STUDIED

Over 6800 patients were enrolled in 32 randomized controlled trials. Most patients were randomized to receive either an anticholinergic or placebo. The trials had variable inclusion and exclusion criteria as well as demographic data. Trial results not in English were translated.

## STUDY DESIGN AND VALIDITY

The researchers performed a meta-analysis of the data from 32 placebo-controlled, double-blinded clinical trials identified in the Cochrane Incontinence Database. These trials compared the effectiveness of anticholinergic medicines (tolterodine, oxybutynin, trospium chloride, propiverine, emepronium bromide, and propantheline) and placebo in treating overactive bladder in men and women.

Symptoms of overactive bladder include urinary urgency, urge urinary incontinence, urinary frequency, and nocturia. These drugs were used in various dosages and were administered either orally or intravesicularly. The authors of this study assessed the methodological quality of these trials and combined the data from the treatment arms and placebo arms of these trials.

The majority of trials did not describe the method of masking allocation to treatment group from the enrolling investigator. Therefore, concealed allocation may not have occurred.

The data analyzed were collected from different points in the drug treatment because some researchers gathered data throughout the trial, while some gathered data only at trial conclusion. This variable length of treatment may have affected symptom control. The trials also did not clearly provide baseline characteristics of enrolled patients, so true trial comparability is unknown. Some results were also reported without measures of variation (eg, confidence intervals), making it difficult for the researchers to evaluate the range of benefit.

## OUTCOMES MEASURED

Primary outcomes were number of leakages, number of voids, and the patients' perception of improvement or cure of their symptoms. Secondary outcomes were volume at first contraction, maximum cystometric capacity, residual volume, and adverse events.

## RESULTS

Treatment decreased episodes of leakage by 1 episode every 2 days and decreased the number of micturitions by 1 every 2 days. Subjects taking anticholinergics also reported fewer subjective symptoms of overactive bladder (relative risk [RR]=1.41; 95% confidence interval [CI], 1.29–1.54). The subjects who received anticholinergics improved maximum cystometric capacity.

No heterogeneity was seen among the trial results. No significant difference in withdrawals due to adverse events was found between drug and placebo groups (RR=1.01; 95% CI, 0.78–1.31).

The most frequently reported adverse effect was dry mouth, which occurred more often in the drug group than the placebo group (RR=2.24–2.92). When elderly patients with polypharmacy were excluded from this analysis, the relative risk of dry mouth increased (2.46–3.36) but the difference was no longer significant.

# MR angiography effective for diagnosing carotid artery stenosis

*Nederkoorn PJ, VanderGraaf Y, Hunink MGM. Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: a systematic review. Stroke 2003; 34:1324–1332.*

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## PRACTICE RECOMMENDATIONS

Magnetic resonance angiography (MRA) is better than duplex ultrasound for diagnosing severe (70%–99%) carotid artery stenosis. Both tests are highly accurate for diagnosing total carotid artery occlusion.

Whether this advantage translates into improved patient outcomes is not known. While cost was not addressed in this study, MRA is 2 to 3 times more expensive than duplex ultrasound.

If cost and effectiveness data support these results, then MRA and duplex ultrasound might replace digital subtraction angiography for carotid artery surgery selection.

## BACKGROUND

Major randomized trials have demonstrated the benefit of carotid endarterectomy for patients with severe symptomatic carotid artery stenosis. This meta-analysis compared duplex ultrasound with MRA and the gold standard, digital subtraction angiography. Because digital subtraction angiography is the standard reference for selecting surgical patients, a noninvasive test with less morbidity and mortality would be preferable.

## POPULATION STUDIED

This meta-analysis included 62 articles yielding 85 separate study populations screened for carotid stenosis with MRA or duplex ultrasound. No information regarding the age, race, or comorbid disorders was given; therefore, it is unknown whether the study population is comparable to a typical family practice setting.

## STUDY DESIGN AND VALIDITY

The authors performed a literature search on PubMed using the keywords "carotid artery" and "angiography" combined with "magnetic resonance" and/or "duplex" or "ultrasound." Additional articles were obtained using the reference lists of original and review publications. Only articles published in English between 1994 and 2001 were included in the search. They also directly contacted authors when data reporting was not sufficient for their analysis.

Two authors independently extracted data from all publications. The analysis was then limited to stenosis of 70% to 99% vs <70%, and 100% stenosis vs <100%. Summary receiver-operator characteristic models were developed to analyze and explain heterogeneity for each diagnostic test and for comparing MRA with duplex ultrasound. A sensitivity analysis demonstrated that the results were not influenced by any particular study.

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The methodology of this study was acceptable. Its strengths included a well-described study inclusion criteria, the use of random-effects modeling to explain statistical heterogeneity between studies, and direct contact with researchers for missing data.

The study's major weaknesses are a limited standardized validity assessment and lack of information on study populations. Minor weaknesses include the use of an arbitrary cutoff date for study inclusion; lack of unpublished studies; and limiting the search to English and only using 1 database (PubMed).

## OUTCOMES MEASURED

The primary outcomes measured where pooled sensitivities and specificities for MRA and duplex ultrasound. No patient-oriented outcomes were measured in this study.

## RESULTS

At a prevalence rate of 1%, MRA showed a sensitivity of 95% with a specificity of 90% (positive likelihood ratio [LR+]=9.5; negative likelihood ratio [LR–]=0.06) for severe stenosis, while duplex ultrasound demonstrated a sensitivity of 86% and a specificity of 87% (LR+ = 6.6; LR– = 0.2). Both MRA and duplex ultrasound were nearly 100% sensitive and specific at determining complete occlusion of the carotid arteries.

Receiver-operator characteristic analysis showed that the performance of MRA for diagnosing severe stenosis depended on the type of MR scanner, while verification bias predicted the performance of duplex ultrasound. Verification bias occurs when the gold standard test (angiography) is ordered on a population of patients with a positive screening test (duplex ultrasound). For diagnosing total occlusion, the same analysis demonstrated no significant heterogeneity for MRA, while verification bias and type of ultrasound scanner explained heterogeneity for duplex ultrasound.

# Warfarin started at 10 mg achieves therapeutic INR faster than 5 mg

*Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. Ann Intern Med 2003; 138:714–719.*

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## PRACTICE RECOMMENDATIONS

Starting warfarin with 10 mg rather than 5 mg achieves a therapeutic international normalized ratio (INR) >1.9 one day earlier (4.2 vs 5.6 days) in selected outpatients at low risk for major bleeding complications with confirmed acute venous thromboembolism.

This strategy saves the time and expense of 1 daily INR determination, and it may decrease the number of days that low-molecular-weight heparin is required by 1 day—although all patients in this study, due to the nature of the design, received a minimum of 5 days of low-molecular-weight heparin.

No conclusions regarding differences in safety or efficacy between the 10-mg and 5-mg nomogram can be drawn from the results of this study, as it was underpowered to detect differences in these important endpoints.

## BACKGROUND

Though not frequently undertaken by family physicians, the treatment of acute venous thromboembolism is now common in the outpatient setting. Patients are treated with a low-molecular-weight heparin, and warfarin is initiated within 24 hours.

This trial compares 2 dosing nomograms that may facilitate safe and timely initiation of warfarin.

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## POPULATION STUDIED

Researchers at 4 Canadian thrombosis clinics enrolled 201 outpatients with confirmed acute venous thromboembolism. Patients ranged in age from 18 to 98 years (mean, 55.5 years), 16% being older than 75 years. After randomization, baseline characteristics of both treatment groups were similar, although the 10-mg group included more men.

Patients were excluded if they had a baseline INR greater than 1.4, had thrombocytopenia, recently received oral anticoagulation, or were at high risk for major bleeding. While the setting was different (specialty clinics), the patients were similar to those seen in family practice offices.

## STUDY DESIGN AND VALIDITY

Subjects were randomly assigned to receive warfarin induction using either a modified, previously developed nomogram[1] starting with 5 mg on the 2 days (n=97) or a new nomogram starting with 10 mg on the first 2 days (n=104). Warfarin was started on the first day of treatment with subcutaneous low-molecular-weight heparin, which was continued for at least 5 days until a therapeutic INR was achieved. Subsequent doses of warfarin were determined from the respective nomograms. INR values were checked on days 3, 4, and 5 in all patients, although the 10-mg nomogram did not require an INR on day 4. Patients were followed for 90 days.

The methodology was very strong and included double-blinding (physician and patient) with concealed allocation (treatment details contained in opaque, sealed envelopes) and intention-to-treat analysis. The study was adequately powered to detect the primary endpoint (time to therapeutic INR), but was underpowered for secondary clinical endpoints.

## OUTCOMES MEASURED

The primary outcome was time in days to a therapeutic INR (>1.9). Secondary outcomes included the proportion of patients with an INR between 2.0 and 3.0 on day 5, total number of INR measurements, incidence of recurrent venous thromboembolism and major bleeding, and survival.

## RESULTS

Patients in the 10-mg group achieved a therapeutic INR 1.4 days earlier than those in the 5-mg group ($P<.001$) and many more patients in the 10-mg group than in the 5-mg group achieved a therapeutic INR by day 5 (83% vs. 46%; $P<.001$; number needed to treat=2.7). As a result, fewer INR assessments were performed in the 10-mg group than in the 5-mg group (8.1 vs. 9.1; $P=.04$). No significant differences were found between the 2 groups in recurrent venous thrombotic events, major bleeding episodes (1 in each group), or survival over the 90 days of follow-up, though the study was not large enough to find a small difference in rates if one exists.

**REFERENCE**

1. Crowther MA, Harrison L, Hirsh J. Warfarin: less may be better (Letter). *Ann Intern Med* 1997; 127:333.

# Oral topiramate effective for alcoholism

*Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomized controlled trial. Lancet 2003; 361:1677–1685.*

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## PRACTICE RECOMMENDATIONS

Oral topiramate is effective in the treatment of alcohol dependence. Patients taking topiramate consumed less alcohol, had fewer heavy drinking days, and had more days abstinent within a 12-week period. This medication adds a significant adjunct to our current treatment of alcoholism and can be considered for use in treating those alcoholics who desire sobriety.

## BACKGROUND

Alcohol dependence is a fairly common problem seen in family practice. To date, there have been few, if any, effective medications that help patients control or reduce their drinking behavior.

Topiramate is an anticonvulsant that inhibits dopamine release in portions of the brain that may be associated with alcohol's rewarding effects. Carbamazepine, another anticonvulsant, has been shown to decrease drinking among patients in alcohol withdrawal programs.[1] This trial tested the efficacy of treatment with topiramate (in addition to counseling) as a method of reducing alcohol consumption and initiating abstinence.

## POPULATION STUDIED

These researchers enrolled 150 patients with alcohol dependence, as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (*DSM-IV*), into the study. They randomly assigned subjects to treatment or placebo groups.

At baseline, the 2 groups did not differ by sex, average number of drinks per day, or age of onset of alcohol abuse. Subjects' average age was 42 years (range, 21–65); 71% were men; 64% white, 32% Hispanic, and 3% African American. Subjects drank an average of 9 drinks per day, with an average 14-year history of alcohol abuse.

Researchers excluded study participants with a positive urine toxicological screen for narcotics, amphetamines, or sedative hypnotics; alcohol withdrawal symptoms; clinically significant physical abnormalities; a history of renal impairment or stones; seizures; or unstable hypertension. They also excluded pregnant or lactating participants and those taking medications affecting alcohol consumption.

Also excluded were study subjects undergoing compulsory treatment for alcohol dependence by an outside agency, subjects treated for alcohol dependence within the 30 days prior to enrollment, or subjects with a current Axis 1 diagnosis other than alcohol or nicotine dependence.

> The anticraving effect of topiramate became more significant towards the end of the study

## STUDY DESIGN AND VALIDITY

Patients were randomly assigned to receive escalating doses of either topiramate (maximum of 300 mg/d) or placebo for a period of 12 weeks. Subjects, clinicians, and those assessing treatment outcomes were blind to group assignment; however, it is unclear whether allocation to the groups was concealed.

Patients also underwent brief behavioral counseling administered by trained nurse practitioners. Researchers did not address whether study participants also underwent other behavioral interventions, such as Alcoholics Anonymous meetings. Researchers used an intention-to-treat approach in their statistical analyses.

## OUTCOMES MEASURED

The investigators measured 6 primary outcomes on a weekly basis throughout the 12 weeks of the study. They assessed the number of drinks per day, drinks per drinking day, heavy drinking days (defined as 5 or more drinks for men or 4 or more drinks for women), and number of days abstinent.

They also measured weekly plasma gamma-glutamyl transferase (GGT) levels, as an objective measure of alcohol consumption, and a secondary efficacy variable of self-reported craving, which they measured with a 14-item obsessive compulsive drinking scale (validated in a previous study of alcoholism severity).[2]

## RESULTS

Patients taking topiramate had an average of 1 fewer drink per day, both on drinking days and on a daily basis, 15% fewer days of heavy drinking, and approximately 12% more days of abstinence compared with the placebo group. The numbers were even more significant at the end of the study, showing a trend in increasing efficacy over the 12 weeks of follow up. The anticraving

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effects were also more significant at the end than when averaged over the length of the study. Plasma GGT levels had a statistically significant drop during the study and obsessive-compulsive drinking scale factor scores decreased significantly. All 150 subjects completed the study, and they reported no adverse events.

**REFERENCES**

1. Malcolm R, Myrick H, Roberts J, Wang W, Anton RF, Ballenger JC. The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. *J Gen Intern Med* 2002; 17:349–355.
2. Moak DH, Anton RF, Latham PK. Further validation of the Obsessive-Compulsive Drinking Scale (OCDS). Relationship to alcoholism severity. *Am J Addict* 1998; 7:14–23.

# Omeprazole and placebo have same long-term effect on dyspepsia

*Rabeneck L, Soucheck J, Wristers K, et al. A double-blind, randomized, placebo-controlled trial of proton pump inhibitor therapy in patients with uninvestigated dyspepsia. Am J Gastroenterol 2002; 97:3045–3051.*

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## PRACTICE RECOMMENDATIONS

Treatment with omeprazole relieved symptoms in the first 2 weeks in about half of patients with dyspepsia—a better response than in the patients treated with placebo. However, by 6 weeks a similar number of patients taking placebo also had symptoms relieved, and at 1 year treatment offered no benefit over placebo.

Additionally, treatment (vs placebo) did not reduce the number of patients who eventually would need endoscopy to investigate the cause of their dyspepsia. Interestingly, treating patients first with either placebo or omeprazole reduced the need for endoscopy by almost half.

## BACKGROUND

Currently, approximately 80% of primary care physicians prescribe a course of antisecretory therapy for patients with uninvestigated dyspepsia, and reserve endoscopy for nonresponders. This strategy is based on a 1985 recommendation by the American College of Physicians.

Recent clinical trials indicate that a *Helicobacter pylori* "test-and-treat" strategy may be preferred, but it benefits only patients with peptic ulcer disease. This study directly addresses the efficacy of 1 initial antisecretory management strategy.

## POPULATION STUDIED

The investigators enrolled 140 patients referred by primary care physicians in a Veterans Administration outpatient clinic. To be eligible, patients had to have uninvestigated dyspepsia of at least 1 week's duration, defined as epigastric or upper abdominal discomfort that was thought to arise from the upper gastrointestinal tract.

Patients were excluded for dyspepsia workup in the prior 6 months, heartburn, history of peptic ulcers, and symptoms or history mandating the need for a prompt diagnostic workup. Patients were almost exclusively male (95%), but were ethnically diverse, with a mean age of 51 years.

## STUDY DESIGN AND VALIDITY

In this double-blind randomized study, participants with uninvestigated dyspepsia received a 6-week course of either omeprazole 20 mg twice daily or matching placebo. Patients were told to discontinue use of any nonsteroidal anti-inflammatory drugs but were allowed to continue taking aspirin (up to 325 mg daily). Patients were supplied with antacid tablets containing alumina, magnesia, and simethicone (Gelusil) for dyspepsia and acetaminophen for pain that was not related to dyspepsia. Patients were evaluated at regular intervals for 1 year.

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The study was large enough to find a difference between treatment and placebo of 15% at 2 weeks, if this difference truly existed. Analysis was performed by intention-to-treat. The patients, the study nurse, and the principal investigator were blinded to treatment assignment. The active and placebo medicines were dispensed in identical-appearing capsules, and treatment allocation was concealed from the study nurse and principal investigator. All patients were properly accounted for, and only 14 of 140 patients were lost to follow-up.

## OUTCOMES MEASURED

The primary outcome was "treatment failure" defined as a Severity of Dyspepsia Assessment (SODA) pain intensity score of ≥29 out of a possible 47 during any follow-up visit. SODA is a standardized reporting tool with 3 scales, which measure pain intensity, nonpain symptoms, and satisfaction with dyspepsia-related health. Secondary outcomes included SODA nonpain scores, SODA satisfaction scores, and endoscopy findings (patients classified as "treatment failures" were advised to undergo endoscopy).

## RESULTS

During the 1 year of follow up, 55.7% of all patients failed treatment and were offered endoscopy. At 2 weeks, there were fewer treatment failures in the omeprazole group (17% vs. 35%, $P$=.037; number needed to treat=6), but at 6 weeks and 1 year this difference was no longer statistically significant.

SODA nonpain and satisfaction scores followed a similar course, with significant improvement in omeprazole-treated patients at 2 weeks but no statistical difference at 1 year.

Of the 78 patients considered to be treatment failures, 70 agreed to undergo endoscopy (36 from the omeprazole group and 34 from the placebo group). There was no difference in the overall distribution of endoscopic findings between these groups.