POEMs®

PATIENT ORIENTED EVIDENCE THAT MATTERS

Practice Recommendations from Key Studies

Candesartan reduces cardiovascular death in CHF patients on ACE inhibitor

McMurray JJV, Östergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003; 362:767–771.

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PRACTICE RECOMMENDATIONS

The addition of candesartan (Atacand) to an angiotensin-converting enzyme (ACE) inhibitor and other treatment reduces cardiovascular death and hospital admissions of patients with congestive heart failure (CHF). As in studies conducted with valsartan (Diovan), candesartan added to an ACE inhibitor does not decrease overall mortality. Clinicians should add candesartan to the medical regimen in nonallergic CHF patients with an ejection fraction of 40% or lower who are already on an optimal dose of an ACE inhibitor.

BACKGROUND

Despite high doses of an ACE inhibitor, some angiotensin II is still produced by the kidney. ARB treatment, in addition to an ACE inhibitor, might offer a benefit. The addition of valsartan to an ACE inhibitor in a previous study decreased cardiovascular mortality but did not affect overall mortality.

A recent study combining valsartan and captopril (Capoten) for patients with a recent myocardial infarction and heart failure showed increased adverse events without any change in survival compared with captopril or valsartan alone.[1] This study evaluated the addition of the ARB candesartan to patients with heart failure already receiving an ACE inhibitor.

POPULATION STUDIED

The investigators enrolled patients aged 18 years or older with left ventricular ejection fraction of 40% or lower and New York Heart Association functional class II–IV CHF who were on optimal, stable doses of ACE inhibitors. Other variables, such as age, race, comorbidities, and medications were similar to typical family practice patients with CHF.

STUDY DESIGN AND VALIDITY

Of the 2548 subjects enrolled, 1276 were assigned to receive candesartan and 1272 to receive placebo. Starting doses were 4 to 8 mg once daily, and the dose was doubled every 2 weeks as tolerated until a target dose of 32 mg

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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. InfoPOEMs, InfoRetriever and POEMS for Primary Care are registered trademarks of InfoPOEM, Inc. POEMS and Patient-Oriented Evidence that Matters are trademarks of InfoPOEM, Inc. These POEMs are copyrighted by, and published with the express permission of InfoPOEM, Inc. and may not be copied or otherwise reproduced without the prior written consent of InfoPOEM, Inc.

Add candesartan to the regimen in nonallergic CHF patients with an ejection fraction <40%

was reached. Patients were seen at 2 weeks, 4 weeks, 6 weeks, 6 months, and then every 4 months until the end of the trial. The median follow-up was 41 months.

The study was well done. Randomization was computer-generated, both subjects and investigators were blinded to treatment assignment, and allocation was concealed. The analysis was intention-to-treat and included all randomized patients. The patient population was mostly male (79%) and of European decent (90%). The randomization scheme ended up placing more smokers in the placebo group (18.5% vs 15.2%), which could have increased the cardiovascular mortality in this group. Almost all (99.8%) patients were followed completely through the study, with only 4 patients lost to follow-up. (*Level of evidence:* **1b**)

OUTCOMES MEASURED

The primary outcome was cardiovascular death or unplanned admission to the hospital for worsening CHF. All-cause mortality and the numbers of hospitalizations for any reason were also measured.

RESULTS

Overall, 483 (37.9%) patients in the candesartan group and 538 (42.3%) in the placebo group experienced the primary outcome of cardiovascular death or unplanned admission to the hospital for worsening CHF (*P*=.011; number needed to treat [NNT]=23 for 41 months).

Taking the outcomes individually, cardiovascular mortality was lower in the treated patients (23.7% vs 27.3%; NNT=28; 95% confidence interval [CI], 13–200), as was the admission rate due to CHF (24.2% vs 28.0%; NNT=26; 95% CI, 12–90). Unlike a previous study with valsartan, patients receiving an ARB, ACE inhibitor, and beta-blocker did not have a higher mortality than patients not receiving a beta-blocker.

Overall all-cause mortality was not improved with the addition of the ARB, which was approximately 30% in both groups. Almost 1 in 4 (24.2%) patients in the candesartan group and 18.3% in the placebo group discontinued the study medication because of an adverse event or abnormal lab value (*P*=.0003). By 6 months systolic blood pressure was lowered by 4.6 mm Hg and diastolic blood pressure by 3.0 mm Hg more in the candesartan-treated group (*P*=.004).

REFERENCE

1. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349:1893–1906.

Vaccinations containing thimerosal do not increase rates of autism

Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA 2003; 290:1763–1766.

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PRACTICE RECOMMENDATIONS

This retrospective cohort study found that autism rates in children receiving vaccines containing thimerosal were not statistically different than for children receiving thimerosal-free vaccines.

This study refutes any connection between the thimerosal preservative and autistic disorders, but does not evaluate the risk of autistic disorders in vaccinated children compared with those who are not vaccinated. No routine pediatric vaccinations currently used in the United States contain thimerosal.

BACKGROUND

Thimerosal has historically been used as a preservative in many vaccines. Thimerosal contains

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ethyl mercury that has been postulated as a cause of neurodevelopmental disorders such as autism. Between 1970 and 1992 the only thimerosal-containing vaccine used in Denmark was the whole-cell pertussis vaccine; after 1992 only a thimerosal-free pertussis vaccine was available.

POPULATION STUDIED

All children born in Denmark between January 1, 1990, and December 31, 1996, were included in this retrospective cohort study. The researchers examined vaccination records for all children and followed the subjects until diagnosis of autism or an autistic-spectrum disorder, age 11 years, or December 31, 2000, whichever came first. A total of 467,450 children were followed for an average of 6.4 years, with 440 cases of autism and 787 cases of autistic-spectrum disorders identified.

STUDY DESIGN AND VALIDITY

Denmark stopped administering vaccines containing thimerosal in June 1992. Through a national registry, the researchers were able to identify how many thimerosal-containing vaccines each child received. All persons in Denmark are given an identification number in the Danish Civil Registration System, thus follow-up information and comparative analyses through links to other databases are readily obtainable and highly reliable.

Diagnosis of autism or an autistic-spectrum disorder was determined from a national psychiatric register. All cases were diagnosed by child psychiatrists prior to addition of the national registry. It is unclear whether the child psychiatrists were blinded to vaccination records prior to diagnosis. (*Level of evidence:* **2b**)

OUTCOMES MEASURED

The primary outcomes were the rate of autism and autistic-spectrum disorders in children vaccinated with thimerosal-containing and thimerosal-free vaccines. A secondary outcome was the change in overall incidence of autism and autistic-spectrum disorder over time.

RESULTS

In this cohort, 95.6% of the children received at least 1 whole-cell pertussis vaccine, with or without thimerosal, during the study period. Autism rates between children vaccinated with thimerosal-containing and thimerosal-free vaccines were similar, with a relative risk of 0.85 (95% confidence interval [CI], 0.60–1.20). Rates of autistic-spectrum disorders were similar in both groups as well, with a relative risk of 1.12 (95% CI, 0.88–1.43).

When comparing children receiving 0, 1, 2, or 3 thimerosal-containing vaccines, there was no evidence of a dose-response correlation between thimerosal and autism or autistic-spectrum disorder. Among all children, the age-adjusted relative risk of diagnosis of autism increased each year from 1990 to 1996

Antidepressant treatment reduces poststroke mortality

Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. Am J Psychiatry 2003; 160:1823–1829.

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PRACTICE RECOMMENDATIONS

Treatment with either fluoxetine or nortriptyline for 12 weeks during the first 6 months poststroke reduced the mortality risk of both depressed and nondepressed patients. Strong consideration should be given to treating clinically depressed and nondepressed poststroke patients who are at significant risk of developing depression (family history or personal history of mood disorders) with antidepressant medication.

BACKGROUND

Depression commonly occurs after an acute stroke and is associated with an increased

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risk of poststroke mortality. It is uncertain to what extent antidepressant treatment reduces this risk.

POPULATION STUDIED

This study enrolled 104 patients between the ages of 26 to 89 years (mean, 69 years) with an acute stroke within the previous 6 months. Patients were excluded if they had any other significant medical illness that would threaten survival or recovery from a stroke, severe comprehension deficit that precluded a verbal interview, history of head injury, or history of brain injury or disease other than a prior stroke.

STUDY DESIGN AND VALIDITY

Patients were randomly assigned (uncertain allocation concealment) to receive fluoxetine, nortriptyline, or placebo unless specific contraindications were present. Fluoxetine was contraindicated for patients with an intracerebral hemorrhage; nortriptyline was contraindicated for patients with a cardiac conduction abnormality or a myocardial infarction within 3 months of the study.

Fluoxetine was given 10 mg/d for weeks 1 to 3, 20 mg/d for weeks 4 to 6, 30 mg/d for weeks 7 to 9, and 40 mg/d for the final 3 weeks. Nortriptyline was given 25 mg/d for week 1, 50 mg/d for weeks 2 and 3, 75 mg/d for weeks 4 to 6, and 100 mg/d for the final 6 weeks. Depression was defined by *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed (*DSM-IV*) criteria for major depressive disorders or minor depressive disorders with a Hamilton depression score of 12 or greater.

Strengths of the study include that it used intention-to-treat analysis, doses of antidepressants were reflective of current practice, outcomes were assessed by individuals blind to treatment group assignment, and all groups were appropriately treated with proper poststroke medical management. Weaknesses of this study included a small sample size, the development subsequent to the study of new treatments for acute stroke such as intravenous and intra-arterial thrombolytics, and no psychiatric follow up beyond the first 2 years poststroke. Results are applicable to the management of poststroke patients seen in a family physician practice. (*Level of evidence:* **1b–**)

Consider antidepressants for all poststroke patients at significant risk of developing depression

OUTCOMES MEASURED

The primary outcome measured was all-cause mortality.

RESULTS

Baseline differences between the groups were minimal: significantly more men were assigned to the fluoxetine group and more women and patients with hemorrhagic stroke assigned to the nortriptyline group.

After 9 years, a total of 50 (48.1%) of the 104 patients had died. Subjects assigned to anti-depressants were significantly more likely to be alive compared with those receiving placebo (59.2% vs 36.4%; P=.03; NNT=4). There were no significant differences in risk factors for cardiovascular disease and concurrent physical illnesses except for diabetes between patients who were still alive and those who had died. Of the 104 patients enrolled, 23 (22%) dropped out before completing the 12-week treatment protocol, with a statistically higher dropout rate (33%) in the fluoxetine group.

There was no significant association between depression at baseline and long-term mortality: 50% of the patients who died were diagnosed with depression at baseline, compared with 57.4% who survived. No difference was seen in survival between the patients assigned to fluoxetine or nortriptyline. Logistic regression model analysis demonstrated that the benefit of antidepressants were significant after controlling for other comorbidities.

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Azithromycin (3 days) better than amoxicillin-clavulanate (10 days) for sinusitis?

Henry DC, Riffer E, Sokol WN, Chaudry NI, Swanson RN. Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis. Antimicrob Agents Chemother 2003; 47: 2770–2774.

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PRACTICE RECOMMENDATIONS

It is reasonable to try a 3-day course of azithromycin (Zithromax) 500 mg/d for patients with a firm diagnosis of acute bacterial sinusitis.

However, keep in mind that antibiotics in general do not provide a clinically meaningful advantage when compared with placebo. Azithromycin is well tolerated, and patients are more likely to complete a 3-day course than a 10-day one. Recall that amoxicillin is as effective as macrolides clinically, and that most cases of sinusitis are not bacterial.

BACKGROUND

Sinusitis is frequently treated with 7- to 14-day courses of antibiotics in primary care; however, several trials have shown success with shorter regimens. This randomized controlled trial compared treatment efficacy using azithromycin for 3 and 6 days with amoxicillin-clavulanate for 10 days.

POPULATION STUDIED

This manufacturer-sponsored, multicenter study, performed in the United States, enrolled 941 adults with acute bacterial sinusitis, defined clinically as presence of either purulent nasal discharge or facial pain, pressure, or tightness for more than 7 but fewer than 28 days, as well as an abnormal plain radiograph. Patients were excluded if they had hypersensitivity to macrolides or penicillins, were receiving systemic antibiotic therapy within 2 weeks prior to enrollment, or had a history of chronic sinusitis.

The average age of the subjects was 41 years; 41% were female; 86% were white, 6% black, and 1% Asian. Most patients had sinusitis symptoms primarily consisting of postnasal purulent discharge, facial pain, and nasal congestion for 13 days prior to enrollment.

STUDY DESIGN AND VALIDITY

This was a double-blind randomized controlled study. Allocation concealment is uncertain. Subjects were assigned to receive azithromycin 500 mg/d for 3 days (AZM-3), azithromycin 500 mg/d for 6 days (AZM-6), or amoxicillin-clavulanate 500 mg/125 mg 3 times daily for 10 days (AMC). The subjects were assessed clinically at baseline, by telephone at day 4, and again clinically at days 10 and 28. Analysis of data was done on an intention-to-treat basis.

The study methodology was fair. Statistically, this study was adequately powered to detect efficacy equivalence rather than superiority between AZM and AMC (the 2 AZM groups were not compared). The researchers did not assess the validity of the criteria used for diagnosis and did not include a placebo arm; nor did they specify the method of allocation.

The fact that the researchers did not include a placebo arm is a severe limitation of this study. Without a placebo arm, there is no way to know if antibiotics were necessary in the first place. A recent double-blind randomized placebo-controlled trial comparing amoxicillin-clavulanate with placebo in adults with acute sinusitis in general practice demonstrated no benefit with antibiotic therapy.[1] (*Level of evidence:* **1b**)

OUTCOMES MEASURED

The primary outcome was cure at the end of trial (28 days), defined as resolution of signs and symptoms to the level that existed prior to the occurrence of the acute illness. Secondary outcomes were adverse reaction to medication and compliance.

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RESULTS

The groups were similar at baseline, and 93.1% followed up at 28 days. In the intention-to-treat population (920 patients), clinical success at 28 days was equivalent among AZM-3 (71.5%), AZM-6 (74.1%), and AMC (71.5%).

Subjects treated with AMC reported a higher incidence of treatment-related adverse events than AZM-3 (51.1% vs 31.1%; *P*=.001; number needed to treat [NNT]=5) or AZM-6 (51.1% vs 37.6%; *P*=.001; NNT=7). Diarrhea was the most frequently reported adverse event, occurring in 17% to 21% of patients treated with azithromycin and 32% of patients treated with AMC. Compliance was significantly better in the AZM groups compared with the AMC group (AZM-3: 99.2%; AZM-6: 93.9%; and AMC: 82.1%).

REFERENCE

1. Bucher HC, Tschudi P, Young J, et al. Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis: a placebo-controlled, double-blind, randomized trial in general practice. *Arch Intern Med* 2003; 163:1793–1798.

Four-year prostate cancer screening interval is effective

Van der Cruijsen-Koeter, van der Kwast TH, Schroder FH. Interval carcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC)-Rotterdam. J Natl Cancer Inst 2003; 95:1462–1466.

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PRACTICE RECOMMENDATIONS

This study found a relatively low rate of prostate cancer diagnoses during a 4-year interval between screenings in Danish men aged 55 to 74 years. For those men choosing to undergo prostate cancer screening, these results show that annual screening is not necessary. Whether screening reduces prostate cancer-specific mortality is yet to be determined.

BACKGROUND

Screening for prostate cancer is still controversial as it has not been shown to decrease mortality. A large randomized screening trial designed to determine screening efficacy is ongoing. Despite uncertain benefit, many men choose to be screened in routine clinical practice. The appropriate interval for prostate cancer screening has not been determined.

POPULATION STUDIED

This study was part of the European Randomized Study of Screening for Prostate Cancer (ERSPC). This analysis used the study arm based in Rotterdam, Denmark, where the researchers enrolled 17,226 men aged 55 to 74 years. There were 8350 men in the screening arm, and 8876 men in the control (unscreened) arm. Other than age, demographics of the study population were not reported.

The study population, while not well characterized by the study authors, is unlikely to include significant numbers of subjects of African descent. This is not a weakness of study design per se, but could impair the applicability of the results to the US population at greatest risk for prostate cancer incidence and mortality. Recruitment procedures were not discussed.

STUDY DESIGN AND VALIDITY

This was a multicenter randomized screening trial. Men in the intervention arm of the study were offered a battery of 3 screening tests for prostate cancer: blood prostate-specific antigen (PSA) level testing, digital rectal exam, and transrectal prostate ultrasound. Initial screenings occurred between October 1993 and December 1996. Repeat screening occurred 4 years later, finishing by December 2000.

Patients with abnormal screening results were referred for prostate biopsy. Ascertainment of patients who developed prostate cancer during the interval between screens (whether case or control) was performed through the Danish national cancer registry. Prostate cancer staging

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and treatment information was obtained through review of hospital records.

Major strengths of this study include the large sample size, randomized design, and the relatively low rate of contamination by "opportunistic" PSA screening among the control population—at least compared with the US general population.[1]

The study also had several weaknesses. Although the investigators and the patients were not blinded, the outcome assessor—the national cancer registry—determined the outcomes and was independent of the study and its investigators. Also, relying on the registry for cancer diagnoses probably underestimates the true incidence due to imperfect case ascertainment.

The applicability of this study to current US screening practice may also be limited by the fact that transrectal ultrasound is not commonly used for prostate cancer screening. Other concerns are that it is not possible to evaluate the appropriateness of recruitment or allocation procedures, and the researchers did not report confidence intervals or other statistical testing for their key results. (*Level of evidence:* **2b**)

OUTCOMES MEASURED

Diagnosis of prostate cancer during the 4-year intervals between screenings.

RESULTS

There were 152 prostate cancers diagnosed among the 8876 control subjects (1.7%), of which 135 were diagnosed within 4 years of randomization. Twenty-five prostate cancers were diagnosed among the 8350 intervention subjects outside of the screening trial—ie, during the 4-year interval between screenings. Twenty-two of these 25 cancers were early stage, and none were metastatic. The sensitivity of the screening regimen in this study was 79.8%.

REFERENCE

1. Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? *JAMA* 2003; 289:1414–1420.

Treatment of high LDL saves lives of those with diabetes or cardiovascular disease

Grover SA, Coupal L, Zowall H, Weiss TW, Alexander CM. Evaluating the benefits of treating dyslipidemia: the importance of diabetes as a risk factor. Am J Med 2003; 115:122–128.

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PRACTICE RECOMMENDATIONS

Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) therapy that effectively reduces low-density lipoprotein (LDL) cholesterol increases life expectancy at least as much among those with diabetes mellitus without cardiovascular disease as among those with established cardiovascular disease alone.

While this result is only based on a validated theoretical model, it was extrapolated to the entire American population, and is consistent with randomized clinical trials. Public health programs and health care providers should give as much emphasis to treating elevated LDL among those with diabetes who are still free of cardiovascular disease as among those with already established cardiovascular disease.

BACKGROUND

It is recommended that patients with diabetes mellitus but without symptomatic cardiovascular disease should receive lipid-lowering therapy to keep LDL levels no more than 100 mg/dL. The authors of this analysis compared life expectancy (years of life saved) by achieving ideal changes in LDL and high-density lipoprotein (HDL) cholesterol among those with diabetes mellitus (but who were free of cardiovascular disease) vs those with previous cardiovascular disease but not diabetes.

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Statin therapy that reduces LDL-C increases life expectancy for patients with diabetes but without CV disease

POPULATION STUDIED

The researchers used their previously validated "Cardiovascular Disease Life Expectancy Model," a Markov-type model, which accurately predicted the cardiovascular mortality observed due to lipid lowering in the Scandinavian Simvastatin Survival Study (4S), among others. In this study, they calculated life expectancy in a theoretical population of patients, aged 30 to 74 years, with either diabetes or cardiovascular disease, based on national prevalence data from the Third National Health and Nutrition Examination Survey (NHANES III).

STUDY DESIGN AND VALIDITY

This model identified risk factors for cardiovascular death (gender, smoking, mean blood pressure, prior cardiovascular disease, age, glucose intolerance, and the natural log of the LDL/HDL ratio) to predict cardiovascular deaths using a survival simulation model. The researchers used NHANES III data to estimate risk factors and cholesterol levels for patients with coronary artery disease or diabetes, and to allow extrapolation to the entire adult US population. They estimated that statins would cause a 35% reduction in LDL and an 8% increase in HDL (as found in the 4S trial). They performed sensitivity analysis including treatment of patients with LDL between 100 and 130, and ending the benefit of statin therapy at age 75.

Similar to other simulation studies, the conclusions drawn depend upon the assumptions in the model. The simulated intervention assumed a baseline LDL level of 211 mg/dL and an HDL level of 43 mg/dL. This study is a theoretical model that accurately predicts the outcomes of populations given statins. However, it can at best only provide an estimate of the effect.

The statin effect on lipid levels was based on that of the simvastatin. This study did not address potential differences on lipid levels, or mortality, from other statins. Another weakness of the study is the lack of any life expectancy estimate for those who had dyslipidemia but neither diabetes nor cardiovascular disease: this would have allowed us to look at the marginal benefit of therapy in those with either diabetes or cardiovascular disease. Although no statistical tests are performed to compare those with cardiovascular disease versus diabetes, the comparison is implied, which could be misleading. Without a proper baseline projection, we cannot determine (when comparing life expectancy for those with diabetes versus cardiovascular disease) whether the projected differences in survival are due to the presence or absence of diabetes, cardiovascular disease or both. (*Level of evidence:* **2b**)

OUTCOMES MEASURED

The researchers predicted years of life saved due to prevention of cardiovascular mortality from use of statins.

RESULTS

The projected benefit of treating dyslipidemia would be similar for US adults aged 30 to 74 with either diabetes alone or cardiovascular disease alone. Men with LDL at least 130 mg/dL and diabetes could expect to gain 3.4 years of life with this therapy, while men with cardiovascular disease could expect to gain 2.7 years. Women with diabetes would gain 2.4 years of life with therapy, while women with cardiovascular disease would gain 2.1 years. The researchers attributed most of the difference in years gained between diabetics and patients with cardiovascular disease to a higher prevalence of smoking in the NHANES III cohort with cardiovascular disease.

If lipid therapy were supplied to subjects with LDL between 100 and 130, or if the benefit of therapy stops at age 75, the lifetime benefit would still be slightly better for those with diabetes. Overall in the US 25.4 million life-years would be saved by giving lipid therapy to those with diabetes, while 16 million years would be saved by giving it to those with cardiovascular disease.

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Conjunctivitis: Diagnostic usefulness of signs and symptoms unknown

Rietveld RP, van Weert HCPM, ter Riet G, and Bindels PJE. Diagnostic impact of signs and symptoms in acute infectious conjunctivitis: systematic literature search. BMJ 2003; 327:789.

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PRACTICE RECOMMENDATIONS

Despite recommendations in ophthalmologic texts for differentiating bacterial from viral conjunctivitis, no research supports the usefulness of any signs or symptoms to make this distinction. This raises validity questions about treatment studies based on clinically diagnosed bacterial conjunctivitis.

BACKGROUND

Primary care providers often prescribe antibiotics based on physical findings of papillary conjunctivitis, mucopurulent discharge, and rapid spread between eyes. However, though often recommended in ophthalmologic texts, the evidence supporting these criteria is unknown.

STUDY DESIGN AND VALIDITY

The researchers searched 4 databases (PubMed, Embase, CINAHL, and Cochrane Controlled Trials Register) and manually searched bibliographies from relevant articles, guidelines, and textbooks to find 2903 articles regarding diagnostic accuracy. They included studies comparing signs, symptoms, or both with bacterial culture.

After they excluded studies of newborns, eye surgery, and *Chlamydia trachomatis* patients, only 1 article remained. The methodology of this study did not hold up to their qualitative data analysis.

One investigator conducted the search, but 2 reviewed the articles. They do not mention how they resolved disagreements (if they existed) about study inclusion. (*Level of evidence:* **1a**)

RESULTS

This systematic review did not find any evidence to support or refute the clinical criteria physicians commonly use to distinguish bacterial from viral conjunctivitis.

DRUG BRAND NAMES

Amoxicillin-clavulanate • Augmentin
Azithromycin • Zithromax
Candesartan • Atacand
Captopril • Capoten
Fluoxetine • Prozac
Nortriptyline • Aventyl, Pamelor
Simvastatin • Zocor
Valsartan • Diovan