Is combining ACE inhibitors and ARBs helpful or harmful?

EVIDENCE-BASED ANSWER

The combination of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has been studied for treatment of heart failure, hypertension, and proteinuric renal disease. Combination therapy with an ACE inhibitor and an ARB decreases symptoms in heart failure patients, but does not appear to have an impact on overall mortality (strength of recommendation [SOR]: **A**).

Preliminary data from small trials indicate that combination therapy may be more effective than monotherapy with an ACE inhibitor or an ARB for lowering blood pressure (SOR: **B**), although morbidity and mortality data for the combination are not currently available. Additionally, in trials involving diabetic and nondiabetic proteinuric renal disease, the combination of ACE inhibitors and ARBs delays progression of renal disease to a greater extent than monotherapy; however, mortality data are also unavailable (SOR: **A**).

EVIDENCE SUMMARY

ACE inhibitors have been used most commonly for the treatment of congestive heart failure and hypertension and to slow the progression of proteinuria. Their primary mechanism of action is the suppression of angiotensin II by blocking its formation via renin and angiotensin I, thereby reducing the main deleterious effects of angiotensin II, which are mediated through vasoconstriction. Other pathways of angiotensin II formation exist and may escape inhibition of the converting enzyme.[1] ARBs block the action of angiotensin II at the AT1 receptor and may, in theory, provide additive benefit.

The data describing the use of the combination of an ACE inhibitor and an ARB in heart failure are from the Valsartan Heart Failure Trial (ValHeFT),[2] the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Trial (CHARM),[3] and in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).[4]

In ValHeFT, 5010 patients with systolic dysfunction were randomized to the ARB valsartan or placebo in addition to background therapy, which included an ACE inhibitor in 93% of subjects. The primary endpoints were mortality and combined mortality and morbidity. An increase in mortality was found among patients on the triple therapy combination of valsartan, an ACE inhibitor, and a beta-blocker (relative risk [RR]=1.4; 95% confidence interval [CI], 1.1–1.9). Among those not on beta-blockers, adding valsartan to baseline therapy of an ACE inhibitor resulted in a modest improvement in the combined endpoint (RR=0.8; 95% CI, 0.7–0.9), but no change in mortality alone was found.[2]

In CHARM, candesartan was added to baseline therapy among patients with heart failure. Baseline therapy included diuretics (90%), beta blockers (55%), spironolactone (17%), and other cardiovascular medications as necessary. In this study, those in the treatment arm had a decrease in the combined endpoint of cardiovascular death plus congestive heart failure admission (RR=0.85; 95% CI, 0.75–0.96), but no difference was seen in overall mortality. Of note, no adverse interaction was demonstrated for those on the triple combination of ACE inhibitors, ARBs, and beta-blockers.[3]

Similarly, VALIANT demonstrated the safety but the lack of incremental efficacy in adding valsartan to ACE inhibitors for patients with left ventricular dysfunction after a myocardial infarction.[4]

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Limited evidence is available from randomized controlled trials on the safety or efficacy of combination therapy exclusively for hypertensive patients. The available published trials were short-term and assessed blood pressure rather than more clinically significant endpoints such as risk of cardiovascular events and mortality. One trial of 177 patients found no significant difference in 24-hour ambulatory mean diastolic blood pressure with combination therapy vs ACE inhibitor or ARB monotherapy, but did show a decrease in clinic diastolic blood pressure.[5] Another small trial of 20 patients demonstrated improved ambulatory blood pressure control with combination therapy vs ACE inhibitor monotherapy.[6]

Several trials have investigated the effect of combination therapy on diabetic and nondiabetic proteinuria. Conclusions from these trials are limited by their small sample size and by measurement of intermediate outcomes without mortality data. The largest trial, COOPERATE, was conducted in Japan and included 336 patients with nondiabetic renal disease.[7] The investigators found that significantly fewer patients receiving combination therapy reached the combined primary endpoint of time to doubling of serum creatinine or end-stage renal disease compared with patients receiving monotherapy. The CALM study included 199 patients with hypertension, micro-albuminuria, and type 2 diabetes mellitus, and demonstrated significantly greater attenuation of urinary albumin/creatinine ratio and significantly improved blood pressure control with combination therapy compared with either therapy alone.[8]

Another trial, ONTARGET, is being conducted to assess the impact of ACE inhibitor or ARB monotherapy and combination therapy on reducing cardiovascular risk; it includes a combined primary endpoint of morbidity and mortality. The study involves 23,400 high-risk patients and will have a follow-up period of 5.5 years. This trial enrolls patients who have coronary disease, cerebrovascular disease, peripheral vascular disease, or diabetes with end-organ damage (inclusion and exclusion criteria are based upon those used in the HOPE study).

RECOMMENDATIONS FROM OTHERS

We were unable to find to find any recommendations regarding the addition of ARB drugs to ACE inhibitors.

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CLINICAL COMMENTARY

Adding ARBs to ACE inhibitors: Good in theory, but clinical evidence is still weak

There is good evidence of the benefits of angiotensin inhibition in multiple diseases, so it is logical to ask if adding receptor blockers adds further benefit. For now, it appears that the addition of an ARB to an ACE inhibitor is an idea that sounds good in theory, but needs more data to prove its clinical benefit and safety.

The clinical evidence for the combo in heart failure and hypertension is weak, since mortality data are lacking and there is the troubling association with increased mortality in the presence of beta blockers. Using the combination is not currently recommended by the major national guidelines for those areas (eg, American Heart Association, Joint National Committee VII). Although the benefit for patients with proteinuria appears promising, we still await evidence for decreasing mortality. Given cost and the combination's uncertain benefit, it would be prudent to wait until the completion of studies currently in progress before we embrace it.

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What are Clinical Inquiries?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists.

Questions chosen are those family physicians vote as most important through a web-based voting system.

Answers are developed by a specific method:

- FPIN medical librarians conduct systematic and standardized literature searches in collaboration with an FPIN clinician or clinicians.
- FPIN clinician authors select the research articles to include, critically appraise the research evidence, review the authoritative sources, and write the answers.
- Each Clinical Inquiry is reviewed by 4 or more peers and editors before publication in JFP.
- FPIN medical librarians co-author each of the Clinical Inquiries that have required a systematic search.
- Finally, a practicing family physician writes an accompanying commentary.

When should we treat isolated high triglycerides?

EVIDENCE-BASED ANSWER

No evidence exists that treating isolated high triglyceride levels in the absence of other risk factors prevents coronary events. Although elevated triglycerides in some studies correlates with coronary events, the association weakens when controlled for factors such as diabetes, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, body mass index, and other cardiac risk factors.

Coincident lowering of triglycerides, while treating other dyslipidemias (such as high LDL and low HDL), can contribute to decreasing coronary events (strength of recommendation [SOR]: **A**, based randomized controlled trials). Treating triglyceride levels over 500 to 1000 mg/dL may reduce the risk of pancreatitis (SOR: **C**, expert opinion).

EVIDENCE SUMMARY

Truly isolated hypertriglyceridemia is rare. To date, no good trials directly address the effect of reducing truly isolated hypertriglyceridemia on cardiovascular morbidity or mortality. High triglycerides are usually accompanied by other features of the "metabolic syndrome" (low HDL, high LDL, insulin resistance, diabetes, hypertension, and obesity), making it almost impossible to look at these in isolation or attribute risk to a specific component.[1]

Whether high triglyceride levels pose risk in the true absence of these other metabolic factors is controversial. One meta-analysis of 17 population-based prospective studies of triglycerides and cardiovascular disease (including 57,000 patients) showed high triglyceride levels to be predictive of cardiac events, even when adjusted for HDL and other risk factors (age, total and LDL cholesterol, smoking, body mass index, and blood pressure).[2] After adjusting for these other risk fac-

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tors, the authors found an increased risk for all cardiac endpoints (myocardial infarction, death, etc) of 14% for men and 32% for women (*Men:* relative risk [RR]=1.14; 95% confidence interval [CI], 1.05–1.28; *Women:* RR=1.37; 95% CI, 1.13–1.66).

Another meta-analysis of 3 prospective intervention trials with 15,880 enrolled subjects found that triglyceride levels did not provide any clinically meaningful information about risk beyond that provided by other cholesterol subfractions.[3]

In treatment trials, the most impressive risk reductions come from the groups who fit the lipid triad of low HDL, high LDL, and high triglycerides. Low levels of HDL appear to interact with hypertriglyceridemia to increase coronary risk, and all studies showing improved outcomes have simultaneously increased HDL while lowering triglycerides.[4–6] In 3 large-scale prospective, placebo-controlled trials (the Helsinki Heart Study, a primary prevention study, and the VA-HIT and Bezafibrate Infarction Prevention trials, both secondary prevention studies), lowering triglycerides and raising HDL concurrently improved outcomes.[5] Successful dietary and medical interventions, especially with statins and fibrates, improved overall lipid profiles—not just triglyceride levels.

Accordingly, elevated triglycerides should prompt providers to rigorously identify these other risk factors for cardiovascular morbidity and mortality, which may not be immediately obvious. In the absence of such other factors, no evidence exists to guide therapy.

Expert opinion[7,8] supported by epidemiologic evidence[9] suggests that patients with triglyceride levels of 500 to 1000 mg/dL may have an increased risk of pancreatitis. Accordingly, providers should consider therapy to lower triglycerides to less than 500 in these patients, regardless of accompanying risk factors.

RECOMMENDATIONS FROM OTHERS

The American College of Physicians, the European Society of Cardiology, and the US Preventive Services Task Force do not recommend screening for hypertriglyceridemia. Clinical guidelines of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III), American Heart Association/American College of Cardiology, and the American Diabetes Association all support LDL lowering as the primary target of therapy based on the patients risk profile.[10] NCEP/ATP III has identified triglyceride levels of <150 as normal, 150–199 as borderline high, 200–499 as high, and ≥500 as very high.[7]

High triglycerides should prompt a search for the "metabolic syndrome" or other secondary causes

A patient with high triglycerides should prompt a search for components of the "metabolic syndrome" and secondary causes, including high dietary fat, high alcohol intake, drugs (steroids, beta-blockers, high-estrogen oral contraceptives), medical conditions (hypothyroidism, nephrosis, renal failure, liver disease, Cushing disease, and lupus), and rare familial dyslipidemias.[7,10,11]

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Our patients are better served when we focus on total coronary risk rather than triglyceride levels

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CLINICAL COMMENTARY

Elevated triglyceride level? First look at the big picture

Observing the pendulum swings of medical knowledge over time is one of the hallmarks of the experienced family physician. As a student, I was warned of the evils of high triglycerides, only to enter a period in the 1970s and 1980s of therapeutic nihilism when triglycerides were not thought to be an independent coronary risk factor.

As outlined here, the pendulum is moving toward a more complex consideration of the effect of triglycerides on heart disease—and what we should do about it. Our patients are better served when we focus on total coronary risk rather than a specific level of triglycerides. An elevated triglyceride level leads me first to look at the glucose. I have found several poorly controlled or even new diabetic patients this way. By then following the adage to "major on the majors and minor on the minors," I have focused on glucose and LDL control to the benefit of my patients.

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Does lowering diastolic BP to less than 90 mm Hg decrease cardiovascular risk?

EVIDENCE-BASED ANSWER

Although lowering diastolic blood pressure (DBP) is associated with reduced cardiovascular events, systolic blood pressure (SBP) is a more robust predictor of cardiovascular risk than DBP and should now be used to diagnose, stage, and treat hypertension.

Lowering diastolic blood pressure (DBP) to <90 mm Hg in hypertensive individuals of all ages decreases the risk of cardiovascular events including myocardial infarction (MI), heart failure, and sudden death (strength of recommendation [SOR]: **A**, based on systematic review of randomized controlled trials). However, there is no consensus regarding how far to lower DBP. A "J-shaped" increase in cardiovascular risks with DBP <85 mm Hg may apply under certain conditions.

EVIDENCE SUMMARY

The concept of a continuous graded relationship between DBP and cardiovascular risk is supported by a meta-analysis of 14 randomized clinical trials showing that lowering DBP by 6 mm Hg reduced the risk of coronary heart disease by 14% (95% confidence interval [CI], 4%–22%; $P<.01$; NNT=200).[1] Throughout the range of DBP in study subjects, 70–115 mm Hg, a lower DBP was associated with a lower risk of coronary heart disease.

However, there is concern that lowering DBP too much may actually increase cardiovascular risk. A 10-year observational study showed that in patients with a history of ischemic heart disease, the incidence of fatal MI was lowest when DBP was between 85 to 90 mm Hg and increased with DBP <85 mm Hg, thus demonstrating a J-shaped curve.[2]

Farnett et al[3] derived a summary curve from 13 studies that stratified cardiovascular outcomes

by level of achieved blood pressure; the nadir of the curve for ischemic heart disease events occurred at 86 to 89 mm Hg DBP. The risk was independent of type of drug therapy, and more pronounced in study subjects with known cardiovascular disease.

A meta-analysis of 7 randomized controlled trials involving 40,233 hypertensive patients used statistical modeling to determine the shape of the "mortality curve" over a range of DBP categories, defined in 10-mm Hg increments from ≤65 to ≥106. The subjects received mainly beta-blockers or thiazide diuretics; controls received placebo or no treatment.[4] Both groups demonstrated increased risk for cardiovascular and all-cause death at the lowest DBP levels. Among treated patients, overall death rate was lowest with a DBP in the range of 76 to 85 mm Hg; among controls the nadir was 86 to 95 mm Hg.

The Hypertension Optimal Treatment (HOT) trial[5] was specifically designed to determine the optimal target blood pressure for hypertensive patients: 18,790 men and women with DBP 100 to 115 mm Hg were randomly assigned to target DBP groups of <90, <85, or <80 mm Hg. All were treated with felodipine and other agents in a stepped-care protocol; average follow-up was 3.8 years. The lowest incidence of cardiovascular events occurred at a mean DBP of 82.6 mm Hg and fewest cardiovascular deaths at 86.5 mm Hg. Further reductions in DBP neither lowered nor increased cardiovascular risk.

A French cohort study[6] followed over 4700 hypertensive men for an average of 14 years. These men had their hypertension treated in usual fashion by their own physicians. In this group, SBP was much more accurate than DBP in classifying severity of hypertension and in predicting cardiovascular risk.

RECOMMENDATIONS FROM OTHERS

The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII)[7] and the World Health Organization–International Society of Hypertension Guidelines[8] state that the relationship between cardiovascular risk and blood pressure is continuous, without a lower threshold. Target blood pressure goals are <140/90 mm Hg in uncomplicated hypertension and <130/80 mm Hg for individuals with diabetes or kidney disease. The National High Blood Pressure Education Program stressed that SBP, not DBP, should become the major criterion for diagnosis and treatment of hypertension.[9]

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CLINICAL COMMENTARY

Emphasize education and focus on systolic blood pressure

In light of JNC VII, there may be some confusion on the part of patients as to "normal" blood pressure and indications for treatment. In fact, on the first page of the NHLBI web site, "Your Guide to Lowering Blood Pressure," the statement is made that "normal blood pressure is less than 120 mm Hg systolic and less than 80 mm Hg diastolic." They later go on to describe the category of prehypertension. It is important to understand the concept and implications of prehypertension, and the "J-shaped" curve in counseling our patients on achieving optimal blood pressure control.

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Which healthy adults should take aspirin?

EVIDENCE-BASED ANSWER

In adults with no history of cardiovascular disease, aspirin reduces the risk of nonfatal myocardial infarction (MI). Aspirin prophylaxis does not decrease all-cause mortality, risk of fatal coronary heart disease, or risk of first stroke (strength of recommendation [SOR]: **A–**, based on multiple randomized controlled trials).

The benefits of aspirin use must be weighed against its potential risks, primarily gastrointestinal bleeding and cerebral hemorrhage. The benefit of aspirin increases with higher levels of cardiovascular risk, while the potential for harm remains relatively constant. Adults with a calculated 5-year coronary heart disease (CHD) event risk of 3% or greater should receive prophylaxis (SOR: **A**, based on multiple randomized controlled trials). The ideal dose of aspirin for prophylaxis is unknown, but it appears that low doses (75–81 mg/d) are as effective as higher doses.

EVIDENCE SUMMARY

The leading cause of morbidity and mortality in the United States is cardiovascular disease (ischemic CHD, stroke, peripheral vascular disease).[1] A meta-analysis of 5 placebo-controlled randomized controlled trials involving more than 50,000 patients free of CHD and stroke evaluated aspirin for primary prevention of cardiovascular disease. Since 3 of the trials excluded women, only 20% of the participants were female. The mean age of participants was 57 years.

The treatment groups took aspirin 75 to 500 mg/d for 3 to 7 years. The meta-analysis found that compared with placebo, aspirin significantly reduced total CHD events (odds ratio [OR]=0.72; 95% confidence interval [CI], 0.60–0.87).[2] Aspirin did not reduce coronary disease mortality (OR=0.87; 95% CI, 0.70–1.09); however, results from 1 study did achieve statistical significance (OR=0.64; 95% CI, 0.42–0.99).[3] No differences were found between aspirin-treated and control groups for all-cause mortality or ischemic stroke reduction.

Aspirin increased the risk of major gastrointestinal bleeding events by almost twofold (OR=1.70; 95% CI, 1.4–2.1). Three of the 5 trials showed no significant increase of intracranial hemorrhage event rates (OR=1.4; 95% CI, 0.9–2.0). Based on combined primary and secondary prevention trials, the risk of intracranial bleeding with aspirin is estimated at 0 to 2 events per 1000 patients per year.[2]

Although the ideal aspirin dosage is uncertain, lower dosages (75–81 mg/d) have been shown to be as beneficial as higher dosages, and may have fewer bleeding complications. Buffered and enteric-coated formulations are no more protective than plain aspirin.[4]

In patients with no known cardiovascular disease, aspirin chemoprevention has been shown to decrease the risk of nonfatal MI and fatal CHD by 28%. At a 5-year CHD risk of 3%, the benefits of prophylaxis outweigh the harms (see **Table**) by 2 to 1—assuming the events of stroke, MI, and bleeding are considered roughly equivalent in severity. (A different threshold may be appropriate for patients that perceive 1 of these events as significantly more serious than the others.) Typical patients at a 3% or greater risk for cardiovascular

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TABLE

Net benefits and harms of aspirin prophylaxis, per 1000 patients

Outcome	Estimated 5-year risk for CHD event		
	1%	3%	5%
All-cause mortality	NS	NS	NS
CHD events avoided	3	8	14
Ischemic strokes avoided	NS	NS	NS
Hemorrhagic strokes	1	1	1
Major gastrointestinal bleeding	3	3	3

NS, not significant

disease include men aged >40 years, postmenopausal women, and younger persons with risk factors for CHD. Physicians determine cardiovascular risk from the presence and severity of risk factors: gender, age, blood pressure, lipid status, diabetes, and smoking status.

Simple risk-assessment tools based on Framingham data are available for computers and palmtop devices (eg, Heart to Heart CV Risk Assessment Calculator, www.meddecisions.com; National Institutes of Health, www.nhlbi.nih.gov/health/prof/heart/). Because only 2 trials included women, it is less clear whether both sexes benefit equally from aspirin prophylaxis.[1]

RECOMMENDATIONS FROM OTHERS

The US Preventive Services Task Force recommends that clinicians discuss aspirin prophylaxis with adults at increased risk for CHD (defined as a 5-year risk of 3% or more). Discussion should include the potential benefits and harms of aspirin therapy.[5]

The American Heart Association recommends low-dose aspirin in people at higher risk of coronary heart disease (especially those with a 10-year CHD risk of 10% or greater).[6] The European Society of Cardiology says there is evidence that low-dose aspirin can reduce the risk of cardiovascular events in asymptomatic high-risk people, such as those with diabetes or well-controlled hypertension, and in men at high multifactorial risk of cardiovascular disease.[7]

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CLINICAL COMMENTARY

Aspirin: effective, safe, inexpensive—and it may prevent heart attacks

Acetylsalicylic acid was first compounded in Germany by chemist Felix Hoffman in 1897. According to information from the Bayer Company, aspirin's cardioprotective effect was first recognized by Dr Lawrence Craven, a California general practitioner. He noted a decreased rate of heart attacks in patients taking this medication.

We now have evidence supporting Dr Craven's astute clinical observation. In adults with no history of cardiovascular disease, aspirin reduces the risk of nonfatal MI. For an individual at a 5-year CHD risk as low as 3%, the benefits of prophylaxis outweigh the harms.

The leading cause of morbidity and mortality in the US is still cardiovascular disease. A simple, effective, safe, and inexpensive preventive measure like recommending aspirin has the potential to prevent heart attacks on a grand scale. A low-dose aspirin per day should be recommended for patients at risk for cardiovascular disease, including men aged >40 years, postmenopausal women, and younger persons with risk factors for CHD. As a 40-something male with a family history of cardiovascular disease reviewing this Clinical Inquiry, I will be taking my aspirin a day.

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Should we screen adults for asymptomatic microhematuria?

EVIDENCE-BASED ANSWER

Screening patients for asymptomatic microhematuria does not appear to improve outcomes, since screening does not identify a population with increased prevalence of urologic malignancy (strength of recommendation [SOR]: **A**, based on prospective cohort studies) or the presence of urologic disease of any type (SOR: **B**, based on 1 cohort study). Asymptomatic microhematuria is sometimes associated with urologic disease that requires intervention to prevent death or disability (SOR: **B**, based on cohort studies). However, no studies demonstrate improved outcomes from screening for asymptomatic microhematuria.

EVIDENCE SUMMARY

Asymptomatic microhematuria is common in adult primary care populations, with a prevalence ranging from 2.5% to 4.3% in 3 studies.[1–3] It is variably associated with urologic disease.

A retrospective cohort study of 2005 British men aged >40 years found 85 (4%) with asymptomatic microhematuria. Subsequent evaluation including intravenous pyelogram and cystoscopy found 2 men with infections—1 with bladder cancer and 1 with polycystic kidneys. Benign prostatic hypertrophy, prostatitis, anatomic abnormalities, and stones accounted for the rest.[3]

A prospective cohort study similarly evaluated 1034 patients with asymptomatic microhematuria found through annual health screening of Japanese adults; 471 (45%) had some urologic diagnosis, including 30 (2.9%) with serious disease (urologic malignancies or progressive glomerulopathy), 195 (18.9%) with moderate disease (such as stones, infection, stable glomerulopathy), and the remainder with less serious disease.[4]

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However, it is unclear whether asymptomatic microhematuria is a useful marker for detecting urologic disease. Two retrospective cohort studies assessed the prevalence of urologic disease in patients with asymptomatic microhematuria compared with those without. Of 501 male steelworkers—an occupation believed to have a higher risk for urologic malignancy—57 men had urologic disease of any type. Six men with urologic disease had asymptomatic microhematuria, while 51 men with urologic disease did not. The correlation between asymptomatic microhematuria and the presence of urologic disease was not significant ($P>.05$). There were 3 cases of urologic cancer in the study, all diagnosed in men without asymptomatic microhematuria.[5]

Among 20,751 California HMO patients who had a periodic health appraisal, screening identified 598 patients with asymptomatic microhematuria (prevalence=2.9%). The medical records for all patients were reviewed for the year prior to screening to find pre-existing urologic disease and then reviewed for new diagnoses over the next 6 years. Three cases of urologic cancer occurred in the group of patients with asymptomatic microhematuria (incidence=0.5%) and 102 cancer cases among the 20,153 patients without asymptomatic microhematuria (incidence=0.5%). Its presence was not significantly associated with either urologic cancers or other serious urologic disease.[2]

No studies demonstrate improved outcomes from screening for asymptomatic microhematuria. Earlier discovery of serious diseases would not often change patient outcome, according to expert opinion.[6,7] Invasive studies, such as intravenous pyelogram and cystoscopy, used to evaluate asymptomatic microhematuria have a rate of serious complications approaching 0.3% (number needed to harm=333).[7]

RECOMMENDATIONS FROM OTHERS

The American Urological Association recommends that all patients with asymptomatic microhematuria be evaluated. However, they do not recommend routine screening for asymptomatic microhematuria to detect urologic malignancy.[8] The US Preventive Services Task Force does not recommend routine screening for bladder cancer by any means, including screening for hematuria.[9]

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CLINICAL COMMENTARY

This poor screening measure is not helpful

A fairly sensitive and specific way to screen for urological malignancies would certainly be worthwhile, but, as this inquiry points out, none exists. The presence of asymptomatic microhematuria in the adult population does not aid in detecting urologic malignancies or any other serious pathology. The incidence of serious disease in the control group is just as high as in the patients with a positive screen for hematuria. A poor screening measure like this one not only is not helpful but also holds the potential to harm patients because of false positive results and the ensuing invasive workups. The USPSTF does not recommend this screening measure.

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What is the best treatment for Osgood-Schlatter disease?

EVIDENCE-BASED ANSWER

Osgood-Schlatter disease is a common cause of pain and tenderness at the tibial tuberosity in active adolescents. It is typically a self-limited condition that waxes and wanes, but which often takes months to years to resolve entirely. It is best managed with conservative measures (activity modification, ice, anti-inflammatory agents) and time (strength of recommendation [SOR]: **B**, several case series and retrospective studies).

In chronic cases that are refractory to conservative treatment, surgical intervention yields good results, particularly for patients with bony or cartilaginous ossicles. Excision of these ossicles produces resolution of symptoms and return to activity in several weeks (SOR: **C**, several case series). Corticosteroid injections are not recommended (SOR: **C**, case reports and expert opinion).

EVIDENCE SUMMARY

No prospective, interventional studies evaluate the treatment of Osgood-Schlatter disease. One case series followed the natural course of the disease in 261 patients (365 symptomatic knees) for 12 to 24 months; 237 (90.8%) patients responded well to restriction of sports activity and nonsteroidal anti-inflammatory agents. The 24 patients who did not improve with conservative measures underwent surgical excision of ossicles, and all returned to normal activities (mean time, 4.5 weeks).[1]

In another case series of 118 patients (151 knees), 88% responded to intermittent limitation of activity (weeks to months) or cylinder casting if limiting activity was ineffective. The remaining 14 patients showed no improvement from these measures; all had surgical excision of an ossicle, sometimes combined with a tubercle-thinning procedure. Only 1 of these patients (7%) did not have complete relief and return to full activities at 6 weeks.[2]

Retrospective analyses also support a conservative approach. One retrospective survey of 68 young athletes with Osgood-Schlatter found they required an average of 3.2 months off all training and 7.3 months of some activity restrictions.[3] In another survey, 20 of 22 (91%) adolescent athletes with Osgood-Schlatter were able to manage their symptoms with ice, aspirin, and mild activity modification. Only 2 needed to stop playing all sports for any period of time, and none required surgery.[4]

Another retrospective review analyzed 50 patients with Osgood-Schlatter (69 knees) for an average of 9 years. No treatments or activity restrictions were recommended. At time of follow-up, 36 (76%) had no limitations, but kneeling continued to be uncomfortable in 60%.[5]

No interventional studies have explicitly evaluated commonly recommended conservative treatments such as ice, analgesics, activity restriction, stretching, strengthening, or anti-inflammatory medication. Corticosteroid injections are generally not recommended, due to case reports of complications, primarily related to subcutaneous atrophy.[6] One small case series demonstrated improvement in Osgood-Schlatter disease pain in 19 of 24 (79%) knees after using an infrapatellar strap for 6 to 8 weeks.[7]

Refractory cases have been treated with a variety of surgical interventions. In 1 case series, 67 patients (70 knees) (mean age 19.6, 77% male) with at least 18 months of symptoms

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despite conservative treatment underwent resection of an ossicle (62 cases) or excision of prominent tibial tubercle (8 cases). These patients were followed for 2.2 years, with 56 (90%) patients with ossicle-resection able to return to maximal sports activity without pain, tenderness, loss of motion, or atrophy.[8]

Another case series compared 22 patients who underwent drilling of the tibial tubercle (with or without the removal of the tibial tubercle) with 22 patients who had excision of loose ossicles or cartilage. Seventeen of the 22 (77%) patients with ossicle excision had complete resolution of symptoms compared with 8 of the 22 (36%) in the patients who underwent tibial tubercle drilling.[9]

One surgical series evaluated excision of tibial tuberosity in 35 patients (42 knees) who did not improve with conservative treatment for an average of 13.25 months. For 37 of 42 knees (88%), patients reported complete relief of pain, and all returned to activity without limitation. The average time to return to sports was 15.2 weeks.[10]

RECOMMENDATIONS FROM OTHERS

The American Academy of Orthopaedic Surgeons and the American Academy of Family Practice recommend activity limitation, ice, anti-inflammatories, protective padding, quadriceps/hamstring strengthening, and time in the management of Osgood-Schlatter disease.[11,12]

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CLINICAL COMMENTARY

Few patients have poor results with conservative measures

Osgood-Schlatter disease is a common problem that all primary care physicians must be ready to recognize and treat. While the research (primarily surgical series) indicates that 10% to 12% of patients may not improve with conservative measures, I have not had nearly that high a percentage of patients who require surgical intervention. Surgery is only offered after the tubercle attaches to the femur, or the tubercle fails to attach at all. In fact, I do not x-ray typical cases of Osgood-Schlatter disease unless evidence suggests patella tendon avulsion, or if parental concern is high. This means that, in most cases, the primary care physician has quite a while to try conservative measures before incurring the expense of radiography or an orthopedic consultation.

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DRUG BRAND NAMES

Candesartan • Atacand
Felodipine • Plendil
Spironolactone • Aldactone
Valsartan • Diovan