Are inhalers with spacers better than nebulizers for children with asthma?

EVIDENCE-BASED ANSWER

Metered-dose inhalers with a spacer (MDI/S) are as good as, or better than, nebulizers for children with asthma. This is based on numerous randomized controlled trials that compared outcomes such as hospital admission rates, asthma severity scores, and pulmonary function scores (strength of recommendation: **A**, based on consistent randomized controlled trials and meta-analysis).

EVIDENCE SUMMARY

A Cochrane review of 10 randomized controlled trials comparing nebulizers with MDI/S, both in adults and in children aged >2 years, showed a substantial trend towards improvement in hospital admission rates with MDI/S use. Sample size for each study was small, ranging from 18 to 152 patients, with a total sample size of 880 children and 444 adults.

The relative risk of admission for MDI/S vs nebulizer for children was 0.65 (95% confidence interval, 0.4–1.06). Secondary outcomes were equivalent or slightly improved, including duration in the emergency department, changes in respiratory rate, blood gases, pulse, tremor, symptoms score, lung function, and use of steroids. Patients with life-threatening asthma (for example, those considered for ventilation) or other chronic illnesses were excluded.[1]

All but 1 of these studies were set in the emergency department and all involved the use of one of a variety of spacers with the MDI, such as the Aerochamber or Inspirease. Whether these efficacy studies can be translated into daily outpatient clinical practice remains unclear. Emergency departments typically have higher staffing levels, and study subjects and their parents may have received more MDI/S training than is practical in many office settings.

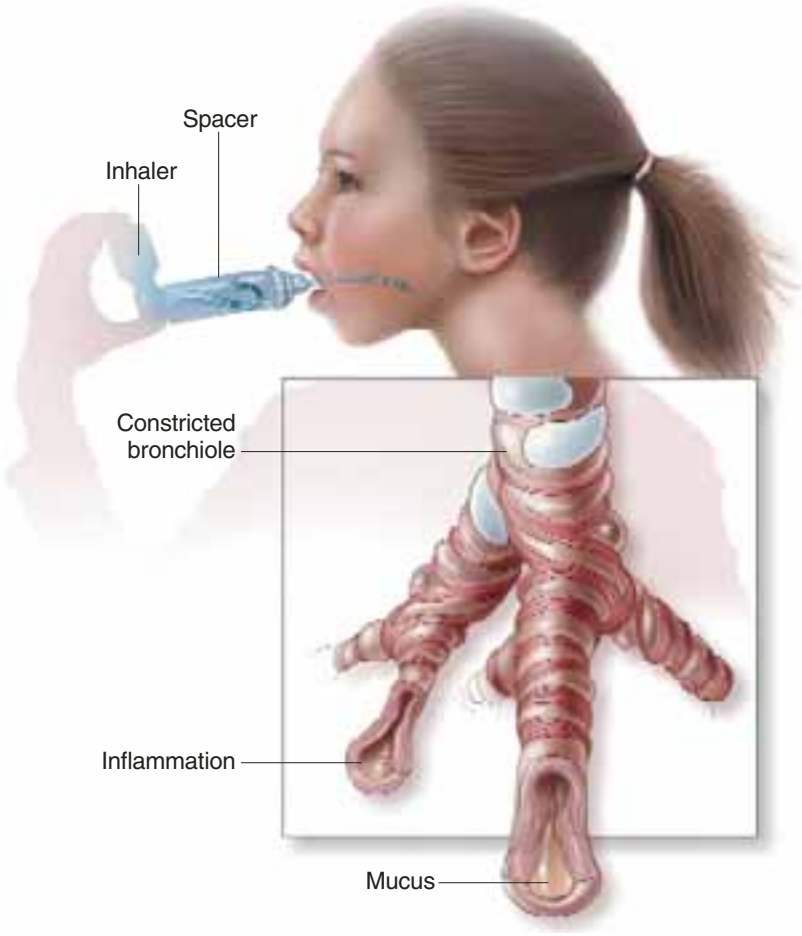
While most of the data were for children aged 2 years and older, 1 study published after the Cochrane review did show a lower admission rate in 85 patients who were 2 to 24 months in the MDI/S group.[2] Controlling for the initial Pulmonary Index score, children using an MDI and Aerochamber spacer were admitted less often (5% vs 20%, number needed to treat=7; P=.05) than children using nebulizers. Since the results of this single small trial are the only data available for this younger age group, using MDI/S instead of nebulizers should be done with caution for children aged <2 years.

Another randomized controlled trial of 152 patients found no difference in primary outcomes of asthma severity score, oxygen saturation, and percent predicted peak expiratory flow rate (PEFR). Several secondary outcomes slightly favored MDI/S: number of treatments given, whether steroids were used, change in heart rate, side effects, rate of hospital admission,and treatment time in the emergency department.[3]

A smaller double-blinded randomized controlled trial of 33 children aged 6 to 14 years showed no difference in MDI/S vs nebulizer, as measured by clinical score, respiratory rate, oxygen saturation, and forced expiratory volume at 1 second (FEV_1).[4] The researchers calculated the study had 90% power to detect a clinically meaningful difference in FEV_1 of 12% of the predicted value between the groups.

Other review articles reach the same conclusion. One article reviewed the literature from 1980 to 1996 and examined 17 prospective clinical trials. Outcomes measured included pulmonary function measures and clinical

FIGURE **MDI with spacer is beneficial when used properly**



Using a spacer with a metered-dose inhaler ensures that patients receive more medication. Be sure they follow these steps:

- Shake the MDI/S several times
- Exhale completely
- Gently but firmly place lips around mouthpiece
- Spray one puff of medicine into the spacer, and inhale slowly and completely
- Hold breath and count to 10 before exhaling

ILLUSTRATIONS BY JENNIFER E. FAIRMAN

scores. The researchers recommended that MDI/S be used due to clinical benefit, safety, lower cost, personnel time, and speed and ease of administration.[5]

A review article from the British literature examined 3 randomized controlled trials involving 51 patients and found no superiority of nebulizer vs MDI/S.[6] A similar review article examined 14 randomized controlled trials for beta-agonist delivery for patients aged 5 to 15 with stable asthma. They found no obvious benefit of 1 type of device over another, including nebulizer, MDI/S, and dry powder inhalers.[7] These last 2 articles claimed to be systematic reviews, although they do not clearly state their search methodology.

Researchers used a wide variety of spacers in all aforementioned studies; accordingly, one cannot be recommended as superior to others. The degree of teaching given to parents and children about MDI/S use was not described in any of the trials.

RECOMMENDATIONS FROM OTHERS

Guidelines from the Global Health Initiative for Asthma, a collaboration of the National Heart, Lung and Blood Institute and the World Health Organization, recommend MDI/S for children with asthma due to increased efficacy and decreased cost (revised in 2002). Specifically, they recommend a spacer with a face mask for infants and preschool children, a mouthpiece and spacer for children aged 4 to 6 years, and a dry powder inhaler or breath-activated device from age 6 onwards.[8] Cincinnati Children's Hospital's

evidence-based guidelines from 1998 also recommend MDI/S for children aged >1 year with acute asthma exacerbations.[9] This guideline suggests using 4 to 8 puffs from a 90 µg albuterol MDI at 1- to 2-minute intervals every 20 minutes for 1 hour, then every 1 to 4 hours subsequently.

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CLINICAL COMMENTARY

Use MDIs with spacers in all but the youngest patients

Until recently, using a nebulizer for the wheezing child or infant seemed intuitively to be the most effective way to deliver bronchodilators. However, with recent data showing that MDIs with spacers are just as effective, I have been using MDIs with spacers for all but my youngest patients. Parents as well as physicians may need to be convinced that using less technology in this case is better for their child. In some cases, parental acceptance of therapy necessitates using a nebulizer.

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Do antipyretics prolong febrile illness?

EVIDENCE-BASED ANSWER

Antipyretics appear to have minor and variable effects on the course of febrile illness. Aspirin and acetaminophen do not prolong the course of rhinovirus illness, although they may prolong the period of viral shedding and worsen nasal congestion (strength of recommendation [SOR]: **A–**, based on small randomized controlled trials).

Acetaminophen did not affect symptoms, overall condition, or time to complete healing in children with varicella, although it increased the time to total scabbing of lesions (SOR: **A**, based on a small randomized controlled trial). Aspirin and acetaminophen may prolong influenza A illness (SOR: **C**, based on a poor-quality, retrospective observational study).

Acetaminophen may prolong the course of *Shigella sonnei* infection (SOR: **B–**, based on a small retrospective cohort study). It does not affect malaria cure rate, and there are insufficient data to assess clearance of *Plasmodium falciparum* (SOR: **C**, based on small randomized controlled trials with heterogeneous results).

EVIDENCE SUMMARY

Acetaminophen has a different mechanism of action from other antipyretics. It halts the production of prostaglandin in the brain but not in

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the periphery, solely lowering fever. Aspirin and other nonsteroidal anti-inflammatory agents inhibit both central and peripheral cyclooxygenase and may cause multiple effects in addition to temperature reduction. Clinical outcome studies of their antipyretic effects are inconclusive.[1]

A randomized controlled trial involving 60 volunteers given intranasal rhinovirus type 2 monitored the effect of aspirin, acetaminophen, ibuprofen, or placebo on virus shedding, immune response, and clinical status. There was no difference in duration of illness. There was a trend toward longer duration of virus shedding in the aspirin and acetaminophen groups, but serum neutralizing antibody response was suppressed ($P<.05$ vs placebo). Aspirin and acetaminophen worsened symptoms of turbinate edema and nasal obstruction ($P<.05$ vs placebo).[2]

In 2 double-blind trials, 45 adults infected with rhinovirus were given aspirin or placebo for 5 days, beginning on the day after viral exposure (as opposed to the typical use in response to symptoms). Aspirin treatment improved symptoms of conjunctivitis significantly, but did not change the duration of illness. Other symptoms (headache, sneezing, chills, malaise, nasal discharge) were not significantly different. Aspirin increased the amount of viral shedding by 36% in 1 trial and 17% in the other ($P<.01$), potentially increasing risk of spread.[3]

In a randomized controlled trial evaluating antipyretic effects on the duration or severity of childhood varicella, 31 children received placebo and 37 received acetaminophen for 4 days. There was no difference in itching, appetite, activity, or overall condition between the 2 groups. Children treated with acetaminophen took 1.1 days longer to total scabbing ($P<.05$), although the number of days until the appearance of the last new vesicle and the time to total healing were unchanged. The duration of viral shedding was not measured, but it is possible that the delay in healing of lesions would prolong viral shedding as well.[4]

A retrospective observational study of 54 volunteers demonstrated prolonged illness in subjects infected with influenza A that received antipyretic therapy. Patients who got antipyretics were sick 3.5 days longer than those who did not (8.8 ± 2.3 days vs 5.3 ± 3.0 days; $P<.001$). Only patients with temperatures >38.9°C on 2 readings 6 hours apart received antipyretics, indicating that the longer course correlated with greater severity of illness as well as with antipyretic use.

In the same study, antipyretics were associated with a trend towards prolonged duration of illness in a group of 21 patients infected with *S sonnei* (4.6 ± 2.1 days with antipyretics vs 1.9 ± 1.6 days without; P=not significant).[5]

A Cochrane review examined 3 trials of acetaminophen vs placebo for fever in 128 adults and children with *P falciparum* malaria. Although fever clearance varied between the trials, the malaria cure rate was similar in all, and the review concluded that data were insufficient to evaluate an effect on parasitemia.[6]

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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.

RECOMMENDATIONS FROM OTHERS

We found no recommendations regarding the use of antipyretics and their effect on the duration of febrile illness.

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CLINICAL COMMENTARY

The risk-benefit ratio of antipyretics may not be as favorable as you think

The doctor's recommendation, "Take two aspirin and call me in the morning," is an enduring stereotype, not an evidence-based therapy for a fever. This review reevaluates the simplistic notion that antipyretics are uniformly beneficial and safe in febrile illnesses.

Surprisingly, there appear to be some negative impacts from using antipyretics for common disease states without much clear benefit. It can be argued that the studies are small and purported negative consequences modest. Still, enough evidence exists to warrant more research and to cause clinicians to consider that the risk-to-benefit ratio of these medications may not be as favorable as once thought.

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Is folate supplementation indicated for patients with CAD?

EVIDENCE-BASED ANSWER

There is insufficient evidence to advocate the routine use of folate supplementation for the treatment of coronary artery disease (CAD). High levels of serum homocysteine have been associated in several studies with an increased risk for CAD (strength of recommendation [SOR]: **B**, associated in case-control studies). Folate supplementation decreases the level of serum homocysteine (SOR: **A**, meta-analysis of randomized controlled trials). This indirect evidence suggests that folate supplementation may be of benefit in slowing the progress of arteriosclerosis.

Two randomized controlled trials measuring the clinical benefits of folate supplementation for patients with CAD have been completed, with differing results. One study showed no benefit of 0.5 mg/d of folate for patients with stable CAD already on statin therapy. The other study found that patients given 1 mg/d of folate with vitamins B_6 and B_{12} had a decreased restenosis rate after percutaneous coronary intervention (PCI) (SOR: **B**, conflicting randomized controlled trials).

It is possible that larger doses of folate are needed to be of clinical benefit, or that the addition of vitamins B_6 and B_{12} are needed for synergy. Several randomized control trials are underway to further assess folate's affect on CAD.

EVIDENCE SUMMARY

Hyperhomocysteinemia is defined as a fasting plasma homocysteine level 15 µmol/L, although levels >10 µmol/L appear to have detrimental effects on risk profiles for CAD and arteriosclerosis.[1] In 22 of 27 retrospective case-control studies, patients with CAD had significantly higher plasma homocysteine levels than control subjects (odds ratio [OR]=1.2–10.9, after adjustment for other CAD risk factors).[2,3] However, only 4 of 7

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prospective nested case-control trials showed a correlation between elevated homocysteine and myocardial infarction (MI) and coronary death.[2]

A meta-analysis of 12 randomized controlled trials found that folate supplementation, with vitamin B_6 and B_{12}, reduces plasma homocysteine levels.[4] However, the long-term clinical cons quences of these interventions are unknown. At doses of 1 gm/d folate has no known side-effects.[5]

Two randomized, placebo-controlled trials of folate reporting clinical endpoints have been completed. One study analyzed folate supplementation in a patient population with known, stable CAD and found no difference in clinical endpoints at 24 months.[6] In this study, 593 patients were randomized to receive either 0.5 mg/d of folic acid or placebo. The primary study endpoint was a composite of events including: overall mortality, sudden death, MI, stroke, and major vascular surgery. The study was powered to detect a 50% reduction in clinical events based on existing observational data in populations with CAD. An event rate of 15% for the 2-year interval was assumed.[6] All patients in this study were on statin therapy prior to initiation of folate supplementation.

The second study analyzed folate supplementation in 553 post-PCI patients. Patients were treated with 1 mg of folate plus 10 mg of vitamin B_6 and 400 µg of vitamin B_{12} for 6 months after the PCI. After a mean follow-up of 11 months, the rate of restenosis requiring revascularization was lower in the vitamin-treated study arm (9.9% vs 16% restenosis rate; relative risk [RR]=0.62; 95% confidence interval [CI], 0.40–0.97; number needed to treat=16).[7] There was also a nonsignificant trend toward fewer deaths and MIs in the treated arm at both 6 and 12 months after intervention (*death:* 1.5% vs 2.8%; RR=0.54; 95% CI, 0.016–1.7; *MI:* 2.6% vs 4.3%; RR=0.60; 95% CI, 0.24–1.51). Statin use was similar in both control (71%) and treatment groups (69%).

RECOMMENDATIONS FROM OTHERS

The American Heart Association and American College of Cardiology do not recommend the routine use of high-dose folic acid or B-vitamin supplements for the primary or secondary prevention of cardiovascular events. The AHA recommendation is to meet recommended daily allowances of folate (400 µg), B_{12} (2.4 µg), and B_6 (1.7 mg) primarily through a balanced diet, with use of supplements if diet alone does not meet the above requirements.[8] Since 1998, wheat flour has been supplemented with folate, adding an estimated 100 µg/day to the average American diet.[8]

The Canadian Task Force on Preventive Health Care (CTFPHC) finds insufficient evidence to advocate screening for hyperhomocysteinemia and rely on expert opinion to advocate treatment in select, high-risk populations.[2] Currently, the CTFPHC advocates meeting the recommended daily allowance of folate, B_{12}, and B_6.[2]

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CLINICAL COMMENTARY

Folate for CAD an unanswered question

Folate seems like a simple, inexpensive, and relatively benign way to improve care. It is no wonder that many physicians have been recommending folate to their patients with CAD for years. However, as responsible physicians, we need more comprehensive evidence on the benefit of folate before making such universal recommendations.

Several points are important: first, most of the evidence on folate is from observational studies. Only 1 interventional study has shown benefit for patients with CAD, and this study used folate in combination with vitamins B_6 and B_{12}. Therefore, if physicians are going to recommend folate supplementation to their patients with CAD, they should recommend this combination rather than folate alone. Also, since this study only included patients who are post-PTCA, it may not apply to all patients with CAD. In short, there is still a fair amount of uncertainty in the answer to this clinical question. We should discuss this uncertainty with our patients, and come to a mutual decision based on preferences.

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Are liver function tests required for patients taking isoniazid for latent TB?

EVIDENCE-BASED ANSWER

Routine liver function test monitoring is not required for all patients on isoniazid therapy for latent tuberculosis (TB) infection (strength of recommendation: **B**, based on case series). No clinical trials have studied the potential risks and benefits of routinely monitoring liver function tests for all patients taking isoniazid for latent TB infection. Data from 2 case series suggest that routine liver function test monitoring leads to withdrawal of isoniazid prophylaxis from about 6% of patients because of abnormal lab results.[1,2] This is 10 to 60 times the hepatitis rate found in case series using a symptom-based monitoring strategy.[3–6] Data are insufficient, however, to conclude that routine liver function test monitoring leads to a lower rate of fatal isoniazid hepatitis compared with a strategy of symptom-based screening. Given that complete recovery from nonfatal hepatitis is the rule, and that patients withdrawn from isoniazid prophylaxis remain at risk for developing active tuberculosis, current evidence does not support routine liver function test monitoring for all patients.

EVIDENCE SUMMARY

Several large population-based case series have tried to define the incidence of isoniazid-induced hepatitis and fatal hepatitis. Because these series differed in patient selection, diagnostic criteria for hepatitis, and toxicity monitoring strategies, and because their data span decades, they provide limited insight. Data from 6 large case series[1,3–7] and 1 pooled compilation of published and unpublished reports[8] are summarized in the **Table**.

Two studies[1,2] that defined hepatitis as asymptomatic liver function test elevation (>5 times normal) on monthly screening found a 6% to 6.4% incidence of hepatitis, a rate 10 to 60 times higher than 4 case series[3–6] that relied on symptom-based monitoring. A pooled analysis of more than 200,000 patients receiving isoniazid prophylaxis and monitored according to 1983 American Thoracic Society guidelines reported an intermediate hepatitis rate (1.2%) and only 2 deaths.[8] Mortality from isoniazid hepatitis is rare, whichever monitoring strategy is selected. Some deaths attributed to isoniazid prophylaxis may also have had other contributing causes, such as unrecognized hepatitis C; most cases and deaths reported in these large series occurred before testing for hepatitis C became available in 1991.

Symptom-based monitoring strategies require stopping isoniazid promptly if symptoms of hepatotoxicity develop. In a series of 62 fatal cases of

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probable or possible isoniazid hepatitis, 42% had been monitored at least monthly for symptoms, and 38% stopped isoniazid within 1 week of symptom onset.[9] Seven of the 8 patients receiving a liver transplant following the development of fulminant, isoniazid-related hepatitis continued to take the drug for a least 10 days after onset of symptoms of hepatotoxicity.[10]

Several series report increasing hepatitis risk with advancing age.[1,3,5,6] In 1 series,[3] rates were 3/1000 in those aged 20 to 34 years, 12/1000 in those aged 35 to 49 years, 23/1000 in those aged 50 to 64 years, and 8/1000 after age 65.

RECOMMENDATIONS FROM OTHERS

The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society joint guidelines for the treatment of latent TB infection state that baseline laboratory testing is not routinely indicated, even for persons aged >35 years, but may be considered for patients who are taking other hepatotoxic medications or have chronic medical conditions.[11]

Baseline measurements of bilirubin and aspartate transaminase (AST) or alanine transaminase (ALT) along with monthly liver function test monitoring are recommended for patients with pre-existing liver disease, patients at risk for chronic liver disease, patients with HIV infection, pregnant or postpartum women, and regular users of alcohol. All patients should be evaluated at least monthly for symptoms of hepatitis, and liver function tests should also be obtained for patients with symptoms compatible with hepatotoxicity. The guideline suggests that isoniazid be stopped if liver function tests exceed 5 times the upper limits of normal, or 3 times the upper limits of normal if the patient is symptomatic. The *Canadian Tuberculosis Standards* (5th ed, 2000) recommend baseline AST before isoniazid preventive therapy is started, and regular monitoring in those with pre-existing liver disease, a history of ethanol abuse, or age ≥35 years.[12]

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CLINICAL COMMENTARY

Patients need to understand risks and benefits of TB treatment

As the number of immigrants increases, FPs will see more patients at high risk for TB. Patients whose risk of developing active TB exceeds the risk of isoniazid toxicity should be tested (targeted testing). It is challenging to ensure an asymptomatic patient completes a 9-month course of therapy while undergoing monthly monitoring for symptoms of isoniazid toxicity. Overall, only 60% of patients complete a full course of isoniazid. Clinical and public health systems that make it easier for patients to follow-up can enhance compliance.

Patients need to understand the benefits of treatment and the symptoms of isoniazid toxicity. The CDC recommends clinical monitoring without routine blood testing for patients of any age without additional risk factors for isoniazid hepatitis. Excessive monitoring can lead to premature discontinuation of therapy because 10%–20% of patients develop some liver function test elevation. The CDC has an excellent course on the basics of latent TB testing and treatment (at www.phppo.cdc.gov/phtn/tbmodules/Default.htm). Patient education materials and risk assessment and monitoring forms can be obtained from state health departments.

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TABLE

INH hepatitis incidence and mortality rates: summary of the largest case series

Study	Time period	Monitoring strategy	Hepatitis definition	No. of patients	No. of hepatitis cases	No. of fatal cases mortality rate
Byrd[1]	~early/mid 1970s	Monthly symptom and LFT screening	AST >5x normal, with or without symptoms	1000	64 (6.4%)	0
Salpeter[8]	1983-early 1990s	Presumed to follow 1983 ATS guidelines[a]	Not defined	202,497	2,459 (1.2%)	2 (0.001%)
Kopanoff[3]	July 1971 to Nov. 1972	Monthly symptom-based screening	AST ≥250 Karmen units or ALT>AST, and no other cause	13,838	92 (0.66%)	8 (0.06%)
IUATCP[4]	mid-1970s	Every-4-week symptom-based screening	Not defined	20,840	95 (0.5%)	3 (0.014%)
Dash[4]	Jan. 1973 to June 1977	Monthly symptom based screening	Jaundice, scleral icterus, or "hepatitis" notation	5300	15 (0.37%)[b]	1 (.019%)
Nolan[6]	Jan. 1989 to 1 December 1995	Monthly symptom-based screening	AST >5x normal with symptoms, and no other cause	11,141	11 (0.1%)	0
LoBue[7]	July 1999 to Nov. 2002	Monthly clinical monitoring, routine LFTs for patients >34 before 2000	LFTs >3x normal with symptoms, *or* LFTs >5x normal without symptoms	3,788	10 (0.3%)	0

[a]Withhold treatment in presence of active liver disease, limit prophylaxis of patients aged >35 to those at highest risk of developing active disease, baseline and periodic LFTs for those over 35, discontinue isoniazid if transaminases exceed 3 to 5 times normal.
[b]Calculation based on life-table analysis, because of high dropout rate during treatment
LFT, liver function test; AST, aspartate transaminase; ALT, alanine transaminase; IUSTCP, International Union Against Tuberculosis Committee on Prophylaxis

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Do ACE inhibitors prevent nephropathy in type 2 diabetes without proteinuria?

EVIDENCE-BASED ANSWER

Angiotensin-converting enzyme (ACE) inhibitors make a significant difference for patients with diabetes as a whole. If patients both with and without microalbuminuria are included together, ACE inhibitors significantly reduce the progression of the albumin excretion rate (strength of recommendation [SOR]: **A**, based on multiple randomized controlled trials) and the development of overt nephropathy (SOR: **A**, based on 1 randomized controlled trial).

However, studying diabetes without microalbuminuria separately, the effect of ACE inhibitors on progression to nephropathy does not reach statistical significance. This applies to both type 1 and 2 diabetes (SOR: **A**, based on randomized controlled trials with heterogenous results). Results are contradictory regarding whether ACE inhibition delays new onset of diabetic microalbuminuria.

EVIDENCE SUMMARY

There are 3 prospective randomized controlled trials studying the effect of ACE inhibitors on albumin excretion for patients with diabetes who do not have microalbuminuria. A 2-year randomized controlled trial compared lisinopril (Prinivil; Zestril) 10 mg/d with placebo in 530 normotensive adults (aged 20–59 years) with insulin-dependent diabetes, defined as those diagnosed with diabetes before age 36 and using continuous insulin therapy within 1 year of diagnosis. At the beginning of the study, 90 patients had microalbuminuria—defined as an albumin excretion rate (AER) >29 mg/24 hr—and 440 patients did not. When the results for all patients who had and did not have microalbuminuria were combined, there was a significantly smaller rise in the AER for the lisinopril group vs the placebo group (3.2 mg/24 hr lower; *P*=.03). However, for the patients without initial microalbuminuria, the reduction in the rise of AER with lisinopril was not significant (1.4 mg/24 hr lower; *P*=.10). The decreased rate of developing new microalbuminuria was also not significant (relative risk reduction [RRR]=12.7%; *P*=.10).[1]

A subsequent trial compared enalapril (Vasotec) 10 mg/d with placebo in 194 normotensive patients (aged 40–60) with type 2 diabetes and without microalbuminuria, defined as AER >30 mg/24 hr. Over the 6-year course of the study, the AER in the placebo group rose from 10.8 mg/24 hr to 26.5 mg/24 hr. The AER of the treatment group dropped from 11.6 mg/24 hr initially to 9.7 mg/24 hr at 2 years, then rose to 15.8 mg/24 hr at 6 years. Enalapril significantly slowed the rise in AER (RRR=0.4; *P*=.001). Nineteen percent of the placebo group developed microalbuminuria, compared with 6.5% of those taking enalapril (absolute risk reduction[ARR]=12.5%; number needed to treat=8; *P*=.042). While this study described a modest and statistically significant renal protective effect of enalapril, it did not use an intention-to-treat analysis.[2]

MICRO-HOPE, a subset of the HOPE trial, studied ramipril (Altace) 10 mg/d vs placebo in 2437 patients with diabetes who did not have clinical proteinuria. Patients were aged 55 years or older and had either a previous cardiovascular event or at least 1 other cardiovascular risk factor. There were 1140 patients with microalbuminuria, defined as an albumin/creatinine ratio ≥2 mg/mmol, and 2437 patients without. After 4.5 years, 10% of patients had developed overt nephropathy, defined as albumin/creatinine >36 mg/mmol.

When all patients in the study were examined together, ramipril provided significant renal protection over placebo (RRR=24%; ARR=1%; *P*=.027). It also lowered the risk of MI by 22%, stroke by

33%, and cardiovascular death by 37%. But in a separate analysis of the patients without microalbuminuria, ramipril did not significantly reduce overt nephropathy (*P*=.50). Ramipril also did not significantly reduce the risk of developing new microalbuminuria in this group (RRR=9%; *P*=.17). Further, for patients without microalbuminuria, ramipril did not reduce the combined outcomes of myocardial infarction, stroke, or cardiovascular death (odds ratio=0.85; 95% CI, 0.70–1.02).[3]

RECOMMENDATIONS FROM OTHERS

We could find no guidelines recommending for or against the use of ACE inhibitors for patients with diabetes without microalbuminuria.

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CLINICAL COMMENTARY

ACE inhibitors should still be used in most patients with type 2 diabetes

ACE inhibitors do not prevent the development of type 2 diabetic nephropathy. In contrast to type 1 diabetes, cardiovascular disease is the primary cause of death in type 2. The HOPE study demonstrated that ACE inhibitor therapy significantly reduces cardiovascular events in type 2 diabetes independent of hypertension status.[4] These benefits are so compelling that the American Diabetes Association strongly recommends ACE inhibitor therapy for type 2 diabetics aged ≥55 years with 1 additional risk factor.[5] Despite not preventing the development of nephropathy, ACE inhibitors should be used for most patients with type 2 diabetes for cardiovascular risk reduction.

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How accurate is stress radionuclide imaging for diagnosis of CAD?

EVIDENCE-BASED ANSWER

Stress radionuclide testing is a moderately accurate test compared with coronary angiography for the diagnosis of coronary artery disease (CAD) in intermediate-risk individuals.

Variations in technique of imaging (planar or single-photon emission computed tomography [SPECT]) and stress (exercise or pharmacologic) do not significantly alter the accuracy of this test, although there is some evidence for decreased accuracy in women (strength of recommendation [SOR]: **A**, based on multiple meta-analyses). Abnormal stress radionuclide screening in vascular surgical candidates also predicts an increased rate of perioperative cardiac events (SOR: **A**, based on meta-analysis).

EVIDENCE SUMMARY

Stress radionuclide imaging—specifically its diagnostic accuracy—has been the subject of numerous studies. Detrano et al[1] reported the first pooled data (56 studies); they concluded that estimates of sensitivity (85%) and specificity (85%) are biased by studies that were not blinded, included subjects with prior myocardial infarction

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TABLE

Diagnostic accuracy reported in meta-analyses of cardiac radionuclide SPECT imaging

Authors, year	Studies	Sn % (95% CI)	Sp % (95% CI)	LR+	LR–
Garber and Solomon 1994[4]	8	88 (73–98)	77 (53–96)	3.8	0.16
Fleischmann et al, et al 1998[5]	27	87 (86–88)	64 (60–68)	2.4	0.20
Kwok et al, 1996[6]	3	78 (69–87)	58 (51–66)	1.9	0.38
Kim et al, 2001[7]	44	90 (89–92)* 89 (84–93)† 82 (77–87)‡	75 (70–79)* 65 (54–74)† 73 (70–79)‡	3.6 2.5 3.0	0.13 0.17 0.25

*Adenosine SPECT
†Dipyridamole SPECT
‡Dobutamine SPECT
SPECT, single-photon emission computed tomography; SN, sensitivity; Sp, specifity; LR+, positive likelihood ratio; LR–, negative likelihood ratio; CI, confidence interval

(MI), or had a work-up (verification) bias (ie, use of the gold standard test is affected by the result on the test under question).

Another systematic review reported estimates of sensitivity ranging from 68% to 96% and specificity from 65% to 100%.[2] The review was accompanied by a position paper from the American College of Physicians stating that the test may be appropriate for a patient with intermediate risk of coronary artery disease.[3]

Four meta-analyses report diagnostic accuracy of radionuclide cardiac imaging (**Table**). Kwok et al[6] analyzed data on women only and found decreased diagnostic accuracy in this population. Kim et al[7] analyzed pharmacologic stressors used with SPECT and confirmed that accuracy is near that of exercise SPECT. Patient-centered outcomes were reported in a meta-analysis of dipyridamole-thallium imaging in the preoperative evaluation of vascular surgery patients. The summary odds ratio for any perioperative cardiac event (in patients with abnormal tests) was 3.5 (95% confidence interval [CI], 2.5–4.8); the odds ratio for MI or cardiac death was 3.9 (95% CI, 2.5–5.6), leading the authors to conclude that there is sound evidence to use radionuclide testing in intermedi.ate-risk patients during preoperative screening.[8]

RECOMMENDATIONS FROM OTHERS

The American Heart Association/American College Cardiology (AHA/ACC) Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures and the American Society of Nuclear Cardiology updated guidelines for cardiac radionuclide imaging in 2003. In this consensus statement (a nonsystematic review of literature and expert opinion), they reported test characteristics to detect a 50% angiographic lesion as follows—exercise SPECT: sensitivity 87%, specificity 73%; vasodilator (adenosine or dipyridamole) SPECT: sensitivity 89%, specificity 75%. They noted that quantitative analysis performs as well as qualitative analysis of radionuclide images. Gated SPECT is slightly more specific and just as sensitive as nongated SPECT.

The Taskforce recommended that radionuclide perfusion scans be performed in patients with

baseline electrocardiogram (ECG) abnormalities (such as left bundle branch block, hypertrophy, digitalis effect, etc), patients who cannot perform an exercise stress test, and to assess the functional effect of indeterminate lesions found on angiography. They also note that the repeat use of radionuclide testing 3 to 5 years after an event in asymptomatic high-risk patients and the initial use of radionuclide testing in patients at very high risk are both somewhat controversial, but the weight of limited evidence suggests some benefit to their use.[9]

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■ CLINICAL COMMENTARY

ECG stress still the choice; image those with abnormal ECG or unable to exercise

Primary care providers frequently face the question of how best to evaluate patients with suspected CAD. Recent studies and expert opinion appear to give conflicting advice regarding the merits of plain exercise ECG vs stress imaging. Information on accuracy doesn't always indicate which test is best for a patient.

Though quoted sensitivities and specificities for exercise ECG typically appear lower than those for stress imaging, costs for stress imaging are significantly higher, and numerous recent studies are demonstrating mortality outcome differences obtainable from physiologic information found in exercise testing (exercise capacity, blood pressure and pulse changes, time to angina).

Currently, the best choice for evaluation appears to be summarized by the 2003 AHA/ACC practice guidelines, which endorse exercise ECG for patients (women included) with intermediate pretest risk, and normal resting ECG for those who are unable to exercise. Stress imaging is cost effective for those patients with abnormal baseline ECG (left bundle branch block, ST abnormalities), or who are unable to exercise.

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