

Evidence-Based Practice

Answering clinical questions with the best sources

VOLUME 12 NUMBER 12 DECEMBER 2009

FROM THE EDITOR

- 3 Party wherever you are

BEHAVIORAL HEALTH MATTERS

- 4 What is the best way to screen for major depressive disorder in patients with dementia?

HELPDESK ANSWERS

- 6 How do you prevent MRSA colonization among close contacts of patients with MRSA skin and soft tissue infections?
- 7 What screening is indicated for patients with a family history of thromboembolism?
- 7 Using statin medications in patients at high risk for coronary artery disease
- 8 How well do BNP levels correspond to response of CHF to therapy?
- 9 When is heparin indicated for the management of acute stroke?
- 10 Probiotics and the prevention of *C difficile*-associated diarrhea in children
- 10 Is there a role for CA-125 in the evaluation of abdominal pain?
- 11 What are the indications for cardiac CT angiography in the evaluation of coronary artery disease?
- 12 Is calcitonin useful for reducing the pain of acute osteoporotic fractures?
- 13 Initial management strategies of dyspepsia in primary care
- 14 Is antiviral therapy for acute, localized herpes zoster safe and effective?

PATIENT EDUCATION

Infants, toddlers, and fruit juice

SPOTLIGHT ON PHARMACY

- 15 What is the efficacy and safety of sinecatechins and imiquimod when treating genital and perianal warts?



IN DEPTH

Warfarin therapy not warranted for secondary prevention of CVD

Warfarin is no better than aspirin for preventing recurrent ischemic strokes.

Bottom Line

No data are available to support the addition or substitution of warfarin after failure of antiplatelet agents for secondary prevention of ischemic stroke. Further, warfarin may be no better than placebo at reducing the risk of noncardioembolic stroke. (Strength of recommendation [SOR] B, based on heterogeneous meta-analyses.)

Background

Noncardioembolic ischemic strokes comprise approximately 60% of all initial and recurrent strokes. The leading cause is thrombotic occlusion of large and medium-sized arteries due to in situ atherothrombosis or atherothromboembolism. A second major cause is thrombotic occlusion of small perforating intracerebral arteries affected by microatheroma and lipid plaque. Cardiac or valvular source strokes account for approximately 20% of all strokes.

Clinically, it is not uncommon to see patients develop new ischemic strokes despite apparently adequate antiplatelet therapy. Would substituting warfarin for antiplatelet therapy (or adding warfarin to ongoing therapy with aspirin or clopidogrel [Plavix]) safely reduce subsequent stroke risk?

Evidence summary

No studies were found that directly address the use of warfarin for tertiary prevention, that is, after the failure of antiplatelet agents for secondary prevention of ischemic stroke. However, a number of studies have evaluated warfarin as a therapy for secondary prevention and compared warfarin with aspirin or even placebo.

The suggestion that warfarin may have clinical value for secondary or perhaps tertiary prevention can be found in the Warfarin-Aspirin Symptomatic Intracranial Disease Study (WASID). This was a retrospective analysis of data from multiple centers of patients

with angiographically proven intracranial large vessel disease. The recurrent stroke rate for patients taking aspirin for secondary stroke prevention was 10.4/100 patient-years. Patients taking warfarin had a stroke rate of 3.6/100 patient-years.¹ No statistical comparisons were available in the article.

To test the effect of warfarin for secondary prevention of ischemic stroke in a prospective fashion, the Warfarin-Aspirin Recurrent Stroke Study (WARSS) was conducted. In this study 2,206 patients with known cerebrovascular disease were randomized to receive either warfarin (target international normalized ratio [INR] 1.4–2.8) or aspirin (325 mg daily). The combined death and recurrent stroke rate over a 2-year period was 16.9%. The 2 treatment groups showed no statistically significant difference in the rate of recurrent stroke. Warfarin was no more effective than aspirin.²

Would using higher doses make a difference? To find out, a prospective randomized trial with 806 patients was conducted using a secondary prevention design similar to the WARSS. It used an INR of 2 to 3 in the warfarin arm and 1,300 mg aspirin daily in the antiplatelet arm. The difference in stroke or vascular death rate was not statistically significant between the 2 groups during the 3 years of follow-up. (In contrast to the WARSS, the combined endpoint of death and recurrent stroke rates was not included).^{3–7}

A 2001 Cochrane meta-analysis analyzed studies of anticoagulation versus antiplatelet therapy for secondary prevention after transient ischemic attack (TIA) or minor stroke of noncardioembolic etiology. Five trials with a total of more than 4,000 patients were included. The studies were divided into high intensity (target INR 3–4.5), medium intensity (target INR 2.1–3.6), and low intensity (target INR 1.4–2.8). Recurrent ischemic stroke risk with anticoagulation at all levels of intensity was no different from that with antiplatelet therapy.⁵

Warfarin management fared even worse in a later Cochrane meta-analysis published in 2003. This meta-analysis compared the safety and effectiveness of anticoagulants with placebo for secondary prevention of cerebrovascular disease. In 11 randomized controlled trials a combined 2,487 patients were randomly assigned to receive anticoagulation (with warfarin or 1 of its analogues) or placebo (not aspirin) after a presumed noncardioembolic ischemic stroke or TIA.⁶

No evidence was found of a statistical effect of anticoagulation therapy for either the odds of death (2 trials, odds ratio [OR] 0.83; 95% confidence interval [CI], 0.52–1.34) or nonfatal stroke, myocardial infarction, or vascular death (4 trials, OR 0.96; 95% CI, 0.68–1.37). Death from any cause (OR 0.95, 95% CI, 0.73–1.24) and death from vascular causes (OR 0.86; 95% CI, 0.66–1.13) were not significantly different between treatment and placebo. No evidence was found of an effect of anticoagulant therapy on the risk of recurrent ischemic stroke (OR 0.85; 95% CI, 0.66–1.09). However, anticoagulants increased fatal intracranial hemorrhage (OR 2.54; 95% CI, 1.19–5.45) and major extracranial hemorrhage (OR 3.43; 95% CI, 1.94–6.08).⁶

Conclusion

Published clinical trials indicate that warfarin is certainly no better than aspirin in the prevention of recurrent ischemic strokes, and may actually be comparable to placebo. Further, aspirin is safer, cheaper, and easier to use. Antiplatelet agents remain the first line in prevention. And despite some theoretical advantages to adding warfarin in cases of recurrence, the difficulty of using the medication safely strongly argues against any such empiric use.

EBP

Long Wong, MD
Dan Criswell, MD

Southwest Oklahoma FMR
Lawton, OK

REFERENCES

- Chimowitz MI, Kokkinos J, Strong J, et al. The Warfarin-Aspirin Symptomatic Intracranial Disease Study. *Neurology*. 1995; 45(8):1488–1493. [LOE 2b]
- Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001; 345(20):1444–1451. [LOE 1a]
- Hankey GJ. Warfarin-Aspirin Recurrent Stroke Study (WARSS) trial: is warfarin really a reasonable therapeutic alternative to aspirin for preventing recurrent noncardioembolic ischemic stroke? *Stroke*. 2002; 33(6):1723–1726. [LOE 2a]
- Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005; 352(13):1305–1316. [LOE 1a]
- Algra A, De Schryer ELLM, van Gijn, Kappelle LJ, Koudstaal PJ. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. *Cochrane Database Syst Rev*. 2001; (4):CD001342. [LOE 2b]
- Sandercock PAG, Mielke O, Liu M, Counsell C. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. *Cochrane Database Syst Rev*. 2003; (1):CD000248. [LOE 2b]
- Chimowitz MI, Lynn M, Howlett-Smith H, et al. Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial: final results [Abstract 2]. Presented at the American Heart Association 29th International Stroke Conference, 2004. *Stroke*. 2004; 35(1):235. [LOE 2b-]

EDITOR-IN-CHIEF

Jon O. Neher, MD
University of Washington

SECTION EDITORS

Drug Profile

Rex Force, PharmD
Idaho State University

Maternity Care

Lee Dresang, MD
University of Wisconsin

Pharmacy HDAs

Connie Kraus, PharmD, BCPS
University of Wisconsin

Behavioral Health Matters

Vanessa Rollins, PhD
University of Colorado

EXECUTIVE EDITOR

John Saultz, MD
Oregon Health Sciences University

Patient Education

Janet Hale, RN
Rockbridge Baths, VA

Dana Abbey, MLS

University of Colorado

Valerie King, MD, MPH

Oregon Health & Science University

Carmen G. Strickland, MD

MAYO Clinic Family Medicine – Thunderbird
Scottsdale, AZ

PRODUCTION

Medical Copy Editor

Melissa L. Bogen, ELS
Chester, NY

Layout and Design

Robert Thatcher
New York, NY

Statement of Purpose

Evidence-Based Practice (EBP) addresses the most important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format.

Newsletter Topics

Transforming Practice: Research evidence on diagnostic testing or treatment periodically accumulates to a "tipping point" that warrants a change in practice. Each month the editors select one topic for which a substantial change in clinical practice seems justified.

HelpDesk: EBP authors search the highest quality sources for best evidence (PrimeEvidence and the TRIPS database) in a concise, clinically useful format.

If definitive answers are not available from these sources, the editors turn to high-quality, well-referenced sources. Other resources are used at the editors' discretion.

Topics in Maternity Care: To keep readers current with trends and new evidence regarding obstetrics and maternity care

Behavioral Health Matters: Presenting the most current evidence related to behavioral and mental health.

Drug Profile: Pharmaceutical information is promoted directly to consumers as well as physicians, and is readily available on the Internet and in other mass media. In each issue of EBP, the editors objectively review the advantages and disadvantages of a featured medication based on scientific evidence.

Patient Education: An evidence-based patient summary of a Clinical Inquiry, provided as a tear-out page to be copied and distributed to your patients.

CME CREDIT

Evidence-Based Practice (2009) has been reviewed and is acceptable for up to 24 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/01/2009. Term of approval is for one year from this date. Each issue is approved for 2 Prescribed credits. Credit must be claimed by March 31, 2010.

Note: Total credit is subject to change based on topic selection and article length.

It is estimated that this educational activity will require 3 hours to complete.

Each physician should claim only those hours of credit that he/she actually spent in the activity.

The learning objectives of the *Evidence-Based Practice* newsletter are to become knowledgeable about evidence-based solutions to commonly encountered clinical problems, to understand how ground-breaking research is changing the practice of family medicine, and to become conversant with balanced appraisals of drugs that are currently being marketed to physicians and/or consumers. The editors of this educational material may review studies that discuss commercial products or devices as well as the unapproved/investigative use of commercial products/devices. The editors of this educational material report that they do not have significant relationships that create, or may be perceived as creating, a conflict relating to this educational material.

Statements and opinions expressed in abstracts and communications herein are those of the author(s) and not necessarily those of the Publisher. The Publisher of this newsletter does not guarantee, warrant, or endorse any methods, product, instructions, procedures, techniques, or ideas mentioned in the newsletter. The Publisher and Editors disclaim any liability, loss or risk, personal or otherwise, which may arise, directly or indirectly, from any use or operation of any methods, products, instructions, procedures, techniques, or ideas contained in the material herein.

Evidence-Based Practice (ISSN 1095-4120) is published monthly by the Family Physicians Inquiries Network, Inc., 409 W. Vandiver Drive, Bldg 4, Suite 202, Columbia, MO 65202. Telephone: 573-256-2066, Fax: 573-256-2078. E-mail: ebp@fpin.org.

Subscription rates for 2009: U.S. Individual \$149, CME upgrade \$75 annually; U.S. Institutions \$159; International Individual \$179; International Institutions \$209. Back issues: U.S. \$17; International \$19. Third Class postage paid at Columbia, MO 65202. The GST number for Canadian subscribers is 124002536. Postmaster: Send address changes to FPIN, Inc., 409 W. Vandiver Drive, Bldg 4, Suite 202, Columbia, MO 65202; Attn: Genny Jacks. Copyright © 2009 by Family Physicians Inquiries Network, Inc.

Party wherever you are

Dear EBP Readers,

To ring in a recent New Year, a well-to-do friend of mine invited me to join a party cruise aboard his new yacht. Not knowing what to expect, I dressed in a quasi-nautical, quasi-formal outfit, put together a seafood appetizer, and traveled through a freezing rain to the marina. Ducking into the yacht's cabin, I began introducing myself to the collected guests and soon my friend declared it was time to shove off for our promised trip around the harbor.

He took the helm, put the big engines in reverse, and instructed all his guests to head topside to toss off the lines. The boat sailed majestically backward about 10 feet when the throttle cable suddenly broke. Immediately my friend dashed into the hold to kill the engines yelling to everyone, "Grab the boat!" The guests who had just cast off the lines were now scrambling in the icy darkness to find the lines again and keep the boat from charging across the marina and rear-ending someone else's 40-foot ego trip.

Slowly the now-wet guests hauled the great wallowing whale back into its slip. The throttle cable could not be fixed. So we crowded into the tiny cabin and, with ice pellets pattering on the deck above, celebrated the arrival of the New Year dockside. It was perhaps a bit of a let down. But I've always said that if you want to party, it really doesn't matter where you find yourself.

As a member of the *Evidence-Based Practice* family, it doesn't really matter where you find yourself either: our virtual end-of-the-year party is in full swing and it is time for all of us to celebrate some awesome productivity. In 2009 with your help, we published 108 new Help-Desk Answers written by 142 contributors from 33 Family Physician's Inquiries Network author programs. We also contributed content to *Global Family Doctor*, *The Teaching Physician*, and *Missouri Family Physician*.

So stay warm and enjoy your accomplishments, any place you happen to be.

Regards,



Jon O. Neher, MD

What is the best way to screen for major depressive disorder in patients with dementia?

Summary

The Cornell Scale for Depression in Dementia (CSDD) is a relatively accurate and well-studied screening tool for depression in patients with dementia. (SOR A, based on validating cohort studies.)

The evidence

Approximately 30% to 40% of elderly patients with dementia will experience depression during the course of their disease.¹ These patients' cognitive, communicative, and behavioral deficits render their depressive traits less obvious. Diagnosing depression becomes increasingly difficult as the level of cognitive impairment worsens. Presently, no gold standard exists for diagnosing depression in patients with dementia.

One validation study compared 2 psychogeriatric depression rating scales, the Geriatric Depression Scale (GDS) in its 4 versions (30, 15, 10, or 4 items), and the Cornell Scale for Depression in Dementia (CSDD, with a cutoff value of ≥ 6) in 145 patients older than 64 years (11 with dementia only, 73 with depression only, 36 with depression and dementia, 36 without depression or dementia).²

In the total population, the CSDD had a sensitivity of 93% and a specificity of 97%, and the 4 GDS versions demonstrated sensitivity ranging from 82% to 90% and specificity ranging from 75% to 94%. The CSDD retained its accuracy as a screening tool for depression in the group with dementia (sensitivity 97%, specificity 100%), whereas the GDS versions lost sensitivity (72%–83%) and specificity (63%–100%) in this population. One limitation of the CDSS is that it requires the presence of a reliable informant (TABLE).²

Another study assessed the prevalence of depression dependent on the severity of dementia by 4 different scales: The GDS-15, the Montgomery-Åsberg Depression Scale (MADRS), the CSDD, and the Nurses Observation Scale for Geriatric Patients (NOSGER).³ The study population consisted of 316 patients with Alzheimer's disease (AD) who were divided into 2 groups: mild AD (Mini Mental State Examination [MMSE] score ≥ 18 , n=157) and moderate-to-severe AD (MMSE < 18, n=159). Internal consistency was good in all scales.

For MADRS and CSDD (cutoff value used ≥ 9), internal consistency was independent of the stage of AD (Cronbach's alpha 0.78–0.85), whereas GDS and NOSGER showed decreased internal consistency with the severity of dementia (Cronbach's alpha 0.63–0.83). Therefore, CSDD and MADRS were found to be the most consistent tools for detecting depression in AD independent of the severity of dementia.³

A 2004 study determined the diagnostic accuracy of 4 brief depression scales—the GDS-15, Even Briefer Assessment Scale for Depression (8-item EBAS DEP), Single Question (“Do you often feel sad or depressed?”), and the CSDD—in an elderly Chinese population with varying degrees of dementia (n=88, 32 with mild dementia and 56 with moderate-severe dementia). The best overall diagnostic tool for detecting depression in dementia was the CSDD (sensitivity 91.7%, specificity 80.0% in mild dementia, sensitivity 70.0%, specificity 87.0% in moderate-to-severe dementia). The Single Question test had a sensitivity of 58.3% and a specificity of 90% in mild dementia, and a sensitivity of 60% and a specificity of 84.8% in moderate-to-severe dementia. The authors concluded that an efficient strategy to diagnose depression in dementia among elderly Chinese patients is to administer the Single Question followed by, when necessary, the CSDD.⁴

EBP

Elizabeth H. Tsai, DO, SM
Jeffrey P. Levine, MD, MPH
Beatrix Roemheld-Hamm, MD, PhD
UMDNJ-RWJMS FMR
New Brunswick, NJ

1. Pfennig A, Littmann E, Bauer M. Neurocognitive impairment and dementia in mood disorders. *J Neuropsychiatry Clin Neurosci*. 2007; 19(4):373–382. [LOE 5]
2. Kørner A, Lauritzen L, Abelskov K, et al. The Geriatric Depression Scale and the Cornell Scale for Depression in Dementia. A validity study. *Nord J Psychiatry*. 2006; 60(5):360–364. [LOE 1b]
3. Müller-Thomsen T, Arlt S, Mann U, et al. Detecting depression in Alzheimer's disease: evaluation of four different scales. *Arch Clin Neuropsychol*. 2005; 20(2):271–276. [LOE 2b]
4. Lam CK, Lim PPJ, Low BL, et al. Depression in dementia: a comparative and validation study of four brief scales in the elderly Chinese. *Int J Geriatr Psychiatry*. 2004; 19(5):422–428. [LOE 1b]

TABLE

Cornell Scale for Depression in Dementia²

Name _____ Age _____ Date _____

Circle one: Inpatient Nursing Home Resident Outpatient

Scoring System

a = Unable to evaluate 0 = absent 1 = mild or intermittent 2 = severe

Ratings should be based on symptoms and signs occurring during the week prior to interview.

No score should be given in symptoms resulting from physical disability or illness.

A. Mood-Related Signs

1. Anxiety: anxious expression, ruminations, worrying	a	0	1	2
2. Sadness: sad expression, sad voice, tearfulness	a	0	1	2
3. Lack of reactivity to pleasant events	a	0	1	2
4. Irritability: easily annoyed, short-tempered	a	0	1	2

B. Behavioral Disturbance

5. Agitation: restlessness, handwringing, hairpulling	a	0	1	2
6. Retardation: slow movement, slow speech, slow reactions	a	0	1	2
7. Multiple physical complaints (score 0 if GI symptoms only)	a	0	1	2
8. Loss of interest: less involved in usual activities (score only if change occurred acutely, ie, in <1 month)	a	0	1	2

C. Physical Signs

9. Appetite loss: eating less than usual	a	0	1	2
10. Weight loss (score 2 if >5 lb lost in 1 month)	a	0	1	2
11. Lack of energy: fatigues easily, unable to sustain activities (score only if change occurred acutely, ie, in <1 month)	a	0	1	2

D. Cyclic Functions

12. Diurnal variation of mood: symptoms worse in the morning	a	0	1	2
13. Difficulty falling asleep: later than usual for this individual	a	0	1	2
14. Multiple awakenings during sleep	a	0	1	2
15. Early morning awakening: earlier than usual for this individual	a	0	1	2

E. Ideational Disturbance

16. Suicide: feels life is not worth living, has suicidal wishes, or makes suicide attempt	a	0	1	2
17. Poor self esteem: self-blame, self-depreciation, feelings of failure	a	0	1	2
18. Pessimism: anticipation of the worst	a	0	1	2
19. Mood-congruent delusions: delusions of poverty, illness, or loss	a	0	1	2

Reprinted from Kørner A, Lauritzen L, Abelskov K, et al. The Geriatric Depression Scale and the Cornell Scale for Depression in Dementia. A validity study. *Nord J Psychiatry*. 2006; 60(5):360-364. Copyright 2006, with permission from Elsevier.

The HelpDesk Search Strategy

HelpDesk Answers are intended to provide the same quality response to a clinical question as would be achieved by a search-savvy physician spending an hour or so on the Internet. Authors of HelpDesk Answers are directed to search Healthlinks (http://healthlinks.washington.edu/search_evidence) and the TRIP database (www.tripdatabase.com). These portals provide access to more than a dozen sources of the highest quality evidence-based clinical information, including BMJ Clinical Evidence, the Guide to Clinical Preventive Services, AHRQ Evidence Reports, and others. Searches of the Cochrane Database, Medline, and other databases, are conducted as needed.

How do you prevent MRSA colonization among close contacts of patients with MRSA skin and soft tissue infections?

Evidence-Based Answer

Standard hand hygiene and contact precautions help prevent methicillin-resistant *Staphylococcus aureus* (MRSA) infection colonization among close contacts of patients with MRSA skin infections. (SOR **C**, based on expert opinion.) It is not clear if nasal mupirocin for patients or patient contacts contributes significantly to community control.

A retrospective study reported on an outbreak of 235 community-acquired MRSA (CA-MRSA) infections among military recruits. The incidence of infection rose from a baseline of 2 cases to 4.95 to 11 cases per 1,000 recruits per month. Upon implementation of a program of increased personal hygiene, use of hand sanitizers, and treatment of nasally colonized persons, the incidence of CA-MRSA infections decreased to baseline within 3 months.¹

A 2003 Cochrane meta-analysis evaluated antimicrobial drugs for treating MRSA colonization. Six trials (with 384 participants) comparing topical or systemic antimicrobials therapy with placebo were included. Four of the studies found no difference in MRSA eradication between the active compound and placebo. One study comparing rifampin with minocycline demonstrated rifampin more effective for eradicating MRSA colonization from all sites at 30 days (relative risk 0.16; 95% confidence interval [CI], 0.02 to 1.00); however, the difference at 90 days was not statistically significant. The development of resistance was noted in all studies, and adverse events were reported in only 3 trials. Fewer adverse events were reported using topi-

cal versus systemic agents. The authors concluded that evidence was insufficient to support use of topical or systemic antimicrobial therapy for eradicating MRSA colonization.²

A 2007 cluster randomized, double-blind, placebo-controlled trial investigated whether intranasal mupirocin therapy could prevent CA-MRSA colonization and infection in a military population. Subjects were followed for the duration of their training period of 16 weeks. A total of 3,447 soldiers were screened and 134 (3.9%) were colonized with CA-MRSA. Staphylococcal soft tissue infection developed in 5 of 65 (7.7%) placebo-treated participants and 7 of 66 (10.6%) mupirocin-treated participants. Of participants not initially colonized with CA-MRSA, 63 of 1,459 of the placebo group and 56 of 1,607 of the mupirocin group developed infections. The difference in the infection rate of the placebo and mupirocin groups was 0.8% (95% CI, -1.0% to 2.7%). Despite short-term CA-MRSA eradication, the study showed no significant decrease in soft tissue infections with mupirocin treatment.³

The CDC in 2006 published strategies for clinical management of MRSA in the community. Standard hand hygiene and contact precautions are strongly encouraged by the expert panel. In patients with recurrence of MRSA or households with several members having active skin infections, decolonization can be considered with intranasal mupirocin applied to the nares twice daily for 5 days or chlorhexidine body washes for 5 to 7 days. Short-term eradication is demonstrated; however, recolonization is common.⁴

Randolph Taylor II, MD
Robert Gauer, MD
Womack FMR Clinic
Fort Bragg, NC

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Medical Department of the U.S. Army or the U.S. Army Service at large.

1. Zinderman CE, Conner B, Malakooti MA, LaMar JE, Armstrong A, Bohnker BK. Community-acquired methicillin-resistant *Staphylococcus aureus* among military recruits. *Emerg Infect Dis*. 2004; 10(5):941-944. [LOE 2b]
2. Loeb M, Main C, Walker-Dilks C, Eady A. Antimicrobial drugs for treating methicillin-resistant *Staphylococcus aureus* colonization. *Cochrane Database Syst Rev*. 2003; (4):CD003340. [LOE 1a]
3. Ellis MW, Griffith ME, Dooley DP, et al. Targeted intranasal mupirocin to prevent colonization and infection by community-associated methicillin-resistant *Staphylococcus aureus* strains in soldiers: a cluster randomized controlled trial. *Antimicrob Agents Chemother*. 2007; 51(10):3591-3598. [LOE 1b]
4. Gorwitz RJ, Jernigan DB, Powers JH, Jernigan JA, and Participants in the CDC-Convened Experts' Meeting on Management of MRSA in the Community. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention. March 2006. http://www.cdc.gov/ncidod/dhqp/pdf/ar/CAMRSA_ExpMtgStrategies.pdf. Accessed November 2, 2009. [LOE 5]

What screening is indicated for patients with a family history of thromboembolism?

Evidence-Based Answer

At present, no clear recommendation can be made for or against routine screening of asymptomatic patients with a high-risk family history of thromboembolism. When such testing is being considered, both the risks and benefits of testing must be presented. Patients can then make an informed decision based on their unique values and circumstances. (SOR **C**, based on expert opinion.)

Several consensus groups, including the American College of Medical Genetics, the American Academy of Pediatrics, and the International Society of Thrombosis and Haemostasis, cite several potential benefits of screening high-risk family members of patients with venous thromboses. Among these benefits:

- Patients can be educated about early signs and symptoms of venous thrombosis.
- Women may be counseled to avoid oral contraceptive therapy.
- Targeted recommendations can be made for anticoagulant therapy in high-risk situations (surgery, prolonged immobilization including prolonged travel, and postpartum states).^{1,2}

Arguments against routine testing of high-risk family members include the following factors:

- Possible denial of insurance, particularly life and disability insurance.
- Inadvertent impact on paternity claims.
- Although inherited thrombophilias are transmitted in an autosomal dominant fashion, the gene mutations are of variable expressivity, so that not all patients with an inherited thrombophilia will develop thrombosis.
- Testing for thrombophilias can be time-consuming and expensive, and has not been proven to be cost effective.³

Additional research is needed to further define the epidemiology of venous thromboembolism in children and adults with familial thrombophilia and to determine the benefits of thromboprophylaxis.³

Results of such research would help determine who and when to screen for thrombophilia, what type of genetic counseling to provide pre- and post-

screening, and what to do with the screening results. Experts agree that the research for screening should continue as new risk factors for thrombophilia are identified and new anticoagulants are developed.

J. Christian Zona, MD, MEd
Flower Hospital FMR
Sylvania, OH

1. Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA; ACMG Factor V Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. *Genet Med*. 2001; 3(2):139–148. [LOE 5]
2. Whitlatch NL, Ortel TL. Thrombophilias: when should we test and how does it help? *Semin Respir Crit Care Med*. 2008; 29(1):25–39. [LOE 5]
3. Thornburg CD, Dixon N, Paulyson-Nuñez K, Ortel T. Thrombophilia screening in asymptomatic children. *Thromb Res*. 2008; 121(5):597–604. [LOE 5]

What is the value of intensive statin therapy in lowering morbidity and mortality in patients at high risk for coronary artery disease?

Evidence-Based Answer

High-dose statins are better at prolonging the time to the first cardiovascular event in patients with diabetes and chronic kidney disease, but not in patients with diabetes who have normal kidney function. (SOR **B**, based on a randomized controlled trial.) High-dose statin therapy reduces the risk of myocardial infarction (MI) and stroke in patients with either acute coronary syndromes (ACS) or stable coronary artery disease (CAD), and has been demonstrated to reduce all-cause mortality in patients with ACS. (SOR **A**, based on a meta-analysis.)

A randomized, controlled, double-blinded study published in 2008 was conducted with 10,002 patients with diabetes mellitus type 2 who either had a normal estimated glomerular filtration rate or chronic kidney disease. The patients were given either 10 or 80 mg atorvastatin.¹

Higher-dose atorvastatin was associated with a reduced risk of first major cardiovascular event at 4.8 years (13.9% [38/273] vs 20.9% [57/273]; hazard ratio=0.65; 95% confidence interval [CI], 0.43–0.98; $P=.04$; number needed to treat=14). The patients with diabetes mellitus and a normal glomerular filtration rate demonstrated no significant treatment effect between the 2 dosing groups.¹

A recent meta-analysis of 7 randomized clinical trials comparing lipid-lowering regimens in 29,395 patients with CAD supports the use of high-dose

statins in a segment of this group.² Nearly one-half of the patients treated with more intensive statin therapy did not achieve a low-density lipoprotein concentration of less than 77 mg/dL; however, the overall risk of MI (odds ratio [OR] 0.83; 95% CI, 0.77–0.91) and stroke (OR 0.82; 95% CI, 0.71–0.95) was decreased. All-cause mortality was reduced 25% in patients experiencing ACS using high-dose statins (based on 353 events in 8,659 patients, OR 0.75; 95% CI, 0.61–0.93). However, no effect on all-cause mortality was noted from high-dose statins in patients with chronic CAD (based on 1,333 deaths in 20,734 patients; OR 0.96; 95% CI, 0.80–1.14). Both ACS and chronic CAD patients exhibited statistically significant benefits from intensive statin therapy on nonfatal MIs (based on 1,772 events in 28,439 patients; OR 0.85; 95% CI, 0.77–0.93) and coronary deaths (based on 839 events in 28,439 patients; OR 0.84; 95% CI, 0.71–0.98). Limitations of this meta-analysis included the lack of homogeneity between the trials.²

Tim Duke, MD
Brice L. Mohundro, PharmD
Baton Rouge General Hospital FMR
Baton Rouge, LA

1. Shepherd J, Kastelein J, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. *Mayo Clin Proc.* 2008; 83(8):870–879. [LOE 1b]
2. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. *CMAJ.* 2008; 178(5):576–584. [LOE 1a]

How well do BNP levels correspond to response of CHF to therapy?

Evidence-Based Answer

B-type natriuretic peptide (BNP)-guided therapy does not alter all-cause hospitalization rates, quality of life, or overall survival compared with symptom-guided therapy, although it does appear to reduce the rate of systolic heart failure–related hospitalizations in patients younger than 74 years. (SOR **B**, based on a randomized controlled trial [RCT].)

A multicenter RCT of 499 patients with ejection fractions $\leq 45\%$ and New York Heart Association (NYHA) class II or greater systolic heart failure (HF) compared outcomes among patients randomized to either a BNP-guided or a symptom-guided treatment strategy.

Patients were evaluated at visits after 1, 3, 6, 12, and 18 months and all received guideline-recommended medical management. Medication doses were adjusted to achieve treatment goals by the 6-month visit, to allow 12 months of outcome observation.¹

Overall survival rates between the BNP and symptom-guided groups were not significantly different (84% vs 78%, respectively; hazard ratio [HR] 0.68; 95% confidence interval [CI], 0.45–1.02; $P=.06$). Survival free of HF-related hospitalization was significantly improved with BNP-guided compared with symptom-guided treatment in younger, but not older, patients (for <75 years age, HR 0.42; 95% CI, 0.24–0.75; $P=.002$; for ≥ 75 years age, HR 0.87; 95% CI, 0.60–1.26; $P=.45$). Quality-of-life scores were similar between the 2 treatment strategies. Rates of adverse events (creatinemia, hypotension) were higher in the ≥ 75 -year age group with BNP-guided therapy (10.5% vs 5.54%; $P=.12$; number needed to harm=20) than in the 60- to 74-year age group with BNP-guided therapy (3.7% vs 4.9%; $P=.74$).¹

In another multicenter RCT, 220 patients (73% male, mean age 65 years) with NYHA class II–III HF under optimum medical management were randomized to BNP-guided therapy or standard (guideline-based) therapy. Outpatient follow-up was monthly for the initial 3 months and then every 3 months, with a median follow-up 15 months. The combined rate for HF-related hospitalization or death was significantly lower with BNP-guided therapy compared with standard therapy (24% vs 57%; $P<.001$; number needed to treat [NNT]=3). Event-free survival was also significantly improved with BNP-guided therapy compared with standard care (84% vs 73%; $P<.01$; NNT=9). All-cause mortality and all-cause hospitalization rates did not differ significantly between groups.²

Current clinical guidelines do not recommend serial measurements of BNP to guide therapy in chronic HF. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines state that using BNP measurements to guide titration of drug doses has not conclusively demonstrated improved patient outcomes more effectively than clinical management with optimization of medications shown in clinical trials to prolong life.³ Similarly, the European Society of Cardiology guidelines state that the use of plasma BNP for monitoring and adjusting drug therapy for chronic HF has not been well estab-



lished.⁴ An Institute for Clinical Systems Improvement Technology Assessment Report likewise states that serial testing of serum BNP to measure treatment response or optimize management of HF has not been shown to have clinical utility.⁵

Malinda Chadsey, MD
Darrell R. Over, MD, MSc
U of AR for Medical Sciences AHEC
Pine Bluff, AR

1. Pfisterer M, Buser P, Rickli H, et al; for the TIME-CHF Investigators. BNP-guided vs symptom-guided heart failure therapy: the trial of intensified vs standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) randomized trial. *JAMA*. 2009; 301(4):383–392. [LOE 1b]
2. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol*. 2007; 49(16):1733–1739. [LOE 1b]
3. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009; 119(14):1977–2016. [LOE 5]
4. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008; 29(19):2388–2442. [LOE 5]
5. Metfessel B, for the Technology Assessment Committee. B-type natriuretic peptide (BNP) for the diagnosis and management of congestive heart failure. ICSI Technology Assessment Report #91. Bloomington, MN: Institute for Clinical Systems Improvement; August 2005. [LOE 5]

When is heparin indicated for the management of acute stroke?

Evidence-Based Answer

Heparin does not appear to improve overall outcomes when used for ischemic stroke or within the first 2 weeks of a cardioembolic stroke. (SOR **B**, extrapolated from meta-analyses of multiple heparinoids.)

A Cochrane review of 24 trials totaling 23,748 patients, aged 28 to 90 years, included studies of patients who received anticoagulant treatment within 2 weeks of acute ischemic stroke, for a duration of up to 1 month, and were followed for up to 1 year.¹ Trials had to have random assignment to control or experimental group, with the following experimental treatments: standard unfractionated subcutaneous or intravenous heparin, low-molecular-weight heparin, subcutaneous or intravenous heparinoid, oral vitamin K antagonists, or thrombin inhibitors. Studies including patients with ischemic stroke due to cerebral venous thrombosis; transient ischemic attacks were not included in the review. Fifteen trials were blind-

ed, whereas 9 were not. Patients excluded from the various trials had a high risk of bleeding, had significant hypertension (excluded from 10 trials), or were comatose (excluded from 9 trials). Aspirin was used in both placebo and experimental groups of 2 trials and was recommended to both placebo and experimental groups in 3 additional trials.

Anticoagulants did not significantly reduce mortality or dependence by the final follow-up (odds ratio [OR] 0.99; 95% confidence interval [CI], 0.93–1.04), but did decrease the odds of pulmonary embolism (OR 0.60; 95% CI, 0.44–0.81) and additional ischemic stroke during the treatment period (OR 0.76; 95% CI, 0.65–0.88). Anticoagulants more than doubled the risk of intracranial hemorrhage (OR 2.55; 95% CI, 1.95–3.33) and tripled the risk of a major extracranial hemorrhage (OR 2.99; 95% CI, 2.24–3.99).¹

A meta-analysis of 7 blinded, randomized controlled trials of 4,624 patients with cardioembolic stroke compared treatment with heparins (subcutaneous or intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, or subcutaneous or intravenous heparinoids) to treatment with aspirin or placebo.² Most patients had atrial fibrillation (n=3,797); the remaining (n=827) had mixed cardioembolic sources of stroke. Patients in the reviewed studies began treatment within 3 to 48 hours of initial stroke, were treated for 5 to 14 days, and were followed for 3 to 6 months.

No significant difference was noted in death or disability when treating patients with heparins versus aspirin or placebo (73.5% vs 73.8%, respectively; OR 1.01; 95% CI, 0.82–1.24). Within 7 to 14 days, no significant reduction was noted in incidence of recurrent stroke using anticoagulants (3% vs 4.9%; OR 0.68; 95% CI, 0.44–1.06), but a significant increase was noted in incidence of intracranial hemorrhage (2.5% vs 0.7%; OR 2.89; 95% CI, 1.19–7.01).²

Shelley Murphy, BHS
José E. Rodríguez, MD
Florida State University
Tallahassee, FL

1. Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2008; (4):CD000024. [LOE 1a]
2. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke*. 2007; 38(2):423–430. [LOE 1a]

Does giving *Lactobacillus* to children at the same time antibiotics are started reduce the incidence of *Clostridium difficile*-associated diarrhea?

Evidence-Based Answer

Probiotics appear to prevent all-cause antibiotic-associated diarrhea (AAD) in children. (SOR **B**, based on heterogeneous randomized controlled trials [RCTs].) However, the effect of probiotics on *C difficile*-associated diarrhea (CDAD) in children is unclear. Further evidence regarding the relative efficacy of the various probiotic agents and dosing are required before a general recommendation can be made regarding their use.

AAD is a common complication of antibiotic therapy, occurring in 5% to 62% of all patients, depending on the antibiotic, duration, and dose.¹ CDAD, a subgroup of AAD that carries significant morbidity, is estimated to be the cause in up to 30% of cases of AAD in adults, but is less common in children.² In 2007, a Cochrane review concluded that while the data are not conclusive, there is evidence that probiotics help prevent AAD in children.¹ Ten studies were included in that review; however, several had small sample sizes with significant dropout rates. Too few documented CDAD cases were available for the authors to draw useful conclusions. They noted, however, that there were no significant adverse effects associated with the use of probiotic agents.¹

One of the stronger studies included in the 2007 Cochrane review was an RCT performed in 2004 to investigate the prevention of AAD in 246 children by the probiotic, *Saccharomyces boulardii*. A secondary measure was the identification of the pathogenesis of AAD cases. Children with acute otitis media or an upper respiratory tract infection were given either 250 mg *S boulardii* daily or placebo for the duration of standard antibiotic therapy. This study showed that 3.4% (4/119) of patients developed AAD in the probiotic group compared with 17.3% (22/127) in the placebo group (relative risk [RR] 0.2; 95% confidence interval [CI], 0.07–0.5; number needed to treat [NNT]=8). Looking specifically at development of CDAD, 2.5% (3/119) of patients developed CDAD in the probiotic group compared with 7.9% (10/127) of patients in the placebo group (RR 0.3; 95% CI, 0.1–1.04), a difference that was not statistically significant.³

Since the Cochrane review, another well-conducted RCT examined the effects of a commercial yogurt

probiotic preparation containing *Lactobacillus casei*, *L bulgaricus*, and *Streptococcus thermophilus* on the prevention of AAD and CDAD in adults. The trial included 135 patients (mean age 74) being treated with antibiotics. Fifty-seven patients were given 100 g of the probiotic yogurt twice a day during and up to 1 week after their antibiotic regimen; 56 patients were given placebo. Twelve patients in the probiotic arm and 10 patients in the placebo arm were lost to follow-up. Ultimately 12% (7/57 patients) developed diarrhea in the probiotic group, compared with 34% (19/56 patients) developed diarrhea in the placebo control ($P=.007$; NNT=5). No patients in the probiotic arm developed CDAD (0/56 patients) compared with 17% (9/53 patients) in the placebo group ($P=.001$). (One patient in the probiotic arm and 3 patients in the placebo control were not tested for *C difficile*.)⁴

At this time, a systematic review is under way to further address this question.⁵

Jonathan KenKnight, BA
David Power, MD, MPH
U of MN Medical School
Minneapolis, MN

1. Johnston BC, Supina AL, Ospina M, Vohra S. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev.* 2007; (2):CD004827. [LOE 1a]
2. McFarland LV, Brandmarker SA, Guandalini S. Pediatric *Clostridium difficile*: a phantom menace or clinical reality? *J Pediatr Gastroenterol Nutr.* 2000; 31(3):220–231. [LOE 5]
3. Kotowska M, Albrecht P, Szajewska H. *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther.* 2005; 21(5):583–590. [LOE 1b]
4. Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ.* 2007; 335(7610):80. [LOE 1b]
5. Johnston BC, Thorlund K. Probiotics for the prevention of *Clostridium difficile* associated diarrhea in adults and children [protocol]. *Cochrane Database Syst Rev.* 2009; (1):CD006095. [LOE 1a]

Is there a role for CA-125 in the evaluation of abdominal pain?

Evidence-Based Answer

CA-125 testing is not specific enough in the primary evaluation of abdominal pain to be clinically useful, and would have unacceptably high false-positive rates. (SOR **B**, based on retrospective studies and reviews.) CA-125 may have a role in the evaluation of abdominal pain in postmenopausal women with a pelvic mass. (SOR **C**, based on expert opinion.)

The tumor-associated antigen CA-125 is a glycoprotein normally expressed in coelomic epithelium during fetal development, which later lines the body cavities and



envelopes the ovaries.¹ More than 2,000 papers have been published concerning the laboratory and clinical studies of CA-125.² Most of the literature references CA-125 clinically to monitor patients with epithelial ovarian cancer. It is helpful to differentiate the use of CA-125 for screening asymptomatic patients from diagnostic use among patients who present with a symptom or abnormality.

CA-125 levels hold little promise as an ovarian cancer screening test in asymptomatic women. A 1993 case-controlled study of 110 women (37 cases and 73 controls) showed the CA-125 had a sensitivity of 24% and specificity of 96% in screening for ovarian cancer in a 15-year period. However, because of the rarity of the disease, even a test with a specificity as high as 99% would result in an unacceptably high number of false-positive test results in a widespread screening program.³

Furthermore, a 2003 literature review on the use of tumor markers found that the positive predictive value of elevated CA-125 is 20% in asymptomatic individuals or individuals with nonspecific complaints, translating to 5 exploratory laparotomies for each ovarian cancer diagnosed, with no effect on survival rate.¹ Another systematic review of screening for ovarian cancer found that after a CA-125 screen, about 3% to 12% of the women were recalled for further testing and assessment, resulting in potential distress and anxiety to otherwise healthy women.⁴

Abdominal pain is a nonspecific symptom and pretest incidence of ovarian cancer is relatively small, even in this subset of patients. A prospective case-control study of 1,055 women seen at 2 primary care clinics who filled out an anonymous symptom survey showed that within a 1-year period, abdominal pain was a reported symptom in 31% (323) of all patients and that ovarian cancer developed in only 2% (22) of these patients (ie, 7% of patients with abdominal pain were later found to have ovarian cancer).⁵ Using the sensitivity of 24% and specificity of 96% derived from the above screening study, the CA-125 test would be expected to have a positive likelihood ratio of 6 and a negative likelihood ratio of 0.8. Applied to this population with abdominal pain, a positive CA-125 would indicate the patient has about a 30% chance of having the disease (still a 70% false-positive rate). A negative test would decrease the incidence of the disease from 7% to 6%.

Experts recommend that the most appropriate use of CA-125 in the evaluation of abdominal pain is for diagnostic evaluation of masses in postmenopausal women, monitoring response to therapy in women with ovarian cancer, and detecting recurrence of ovarian malignancy.¹⁻⁴ To date, no medical organization recommends the use of CA-125 in evaluating abdominal pain or as a means to generally screen for cancer.

Robert J. Campbell, MD
Suzanne Nagy, MSLS
Emily Lagergren, BS
Florida State University
Tallahassee, FL

1. Perkins GL, Slater ED, Sanders GK, Prichard JG. Serum tumor markers. *Am Fam Physician*. 2003; 68(6):1075-1082. [LOE 5]
2. Bast RC Jr, Xu FJ, Yu YH, Barnhill S, Zhang Z, Mills GB. CA 125: the past and the future. *Int J Biol Markers*. 1998; 13(4):179-187. [LOE 5]
3. Helzlsouer KJ, Bush TL, Alberg AJ, Bass KM, Zacur H, Comstock GW. Prospective study of serum CA-125 levels as markers of ovarian cancer. *JAMA*. 1993; 269(9):1123-1126. [LOE 3B]
4. Bell R, Petticrew M, Luengo S, Sheldon TA. Screening for ovarian cancer: a systematic review. *Health Technol Assess*. 1998; 2(2):i-iv, 1-84. [LOE 1A]
5. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA*. 2004; 291(22):2705-2712. [LOE 3B]

What are the indications for cardiac CT angiography in the evaluation of coronary artery disease?

Evidence-Based Answer

Cardiac computed tomography angiography (CCTA) may be considered in the evaluation of symptomatic patients with intermediate pretest probability of coronary artery disease (CAD) and without previous revascularization, if stress testing cannot be performed or is inconclusive. (SOR **B**, based on a systematic review of conflicting evidence.) CCTA may also be useful in the immediate evaluation of patients presenting to the emergency department with acute chest pain who have negative biomarkers and are at low to intermediate cardiac risk. (SOR **A**, based on a meta-analysis.)

An expert writing committee of the American Heart Association (AHA) has published recommendations on the use of CCTA in imaging coronary arteries.¹ Evidence was gathered through an English language search of Medline between 1990 and 2006. The writing group selection process, the study selection criteria, and the methods for formulating the recommendations were not described. No meta-analyses were attempted.

CONTINUED

For a stenosis >50%, the AHA stated that most studies of CCTA yield negative predictive values of 98% to 100% (corresponding to negative likelihood ratios of 0.01–0.15). Therefore the use of CCTA in symptomatic patients with intermediate pretest probability of CAD, including patients with equivocal stress test results, is classified by the AHA as a class IIa recommendation (“conflicting evidence” but “weight of evidence/opinion is in favor of usefulness/efficacy”).¹ This recommendation is based on “B” level of evidence (“data derived from a single randomized trial or nonrandomized studies”). The use of CCTA in patients with low pretest probability of CAD is not indicated, because concerns regarding radiation dose outweigh diagnostic benefits. Patients with high pretest probability of CAD are more likely to need percutaneous intervention and should receive conventional coronary angiography (class III recommendation, “procedure/treatment is not useful/effective and in some cases may be harmful,”¹ and level of evidence C, “only consensus opinion of experts, case studies, or standard of care”). Use of CCTA in patients after stent revascularization is not recommended, due to artifact from the stent material precluding evaluation of up to 49% of stents.

A subsequent meta-analysis of 9 studies (566 patients) investigated the diagnostic performance of CCTA in the emergency room setting for patients with acute chest pain suspected of having acute coronary syndrome, but negative initial cardiac markers.² Included studies, found through a comprehensive literature search, defined a positive CCTA as a stenosis >50%; studies used conventional angiography or clinical follow-up as reference standards. The pooled sensitivity and specificity were 95% (95% confidence interval [CI], 90%–98%) and 90% (95% CI, 87%–93%). The pooled negative likelihood ratio was 0.12 (95% CI, 0.06–0.21) and the positive likelihood ratio was 8.60 (95% CI, 5.03–14.70), indicating CCTA may be useful in excluding significant CAD in patients with low to intermediate pretest probability. In patients with high pretest probability, a negative CCTA would not adequately rule out significant CAD.

The relatively small number of patients and lack of direct comparison with other diagnostic algorithms suggest further research is needed to clarify the indication for CCTA in acute coronary syndrome.

Suhail Jafrey, MD
Thomas Satre, MD

U of MN/St. Cloud Hospital FMR
St. Cloud, MN

1. Bluemke DA, Achenbach S, Budoff M, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. *Circulation*. 2008; 118(5):586–606. [LOE 1a]
2. Vanhoenacker PK, Decramer I, Blatt O, Sarno G, Bevernage C, Wijns W. Detection of non-ST-elevation myocardial infarction and unstable angina in the acute setting: meta-analysis of diagnostic performance of multi-detector computed tomographic angiography. *BMC Cardiovasc Disord*. 2007 Dec 19; 7:39. [LOE 1a]

Is calcitonin useful for reducing the pain of acute osteoporotic fractures?

Evidence-Based Answer

Calcitonin has been shown to improve acute pain at rest in patients with osteoporotic vertebral fractures, when compared with placebo, and reduce the use of other analgesic medications (SOR **A**, based on a meta-analysis of randomized controlled trials [RCTs]). However, calcitonin is not superior to placebo in patients with hip fracture who have undergone surgical repair. (SOR **B**, based on an RCT.)

A 2005 meta-analysis of 5 RCTs included 246 patients with acute pain from an osteoporotic vertebral fracture.¹ The average age was 72 years and 56% were female. Four studies examined pain levels among patients taking calcitonin compared with placebo.

After 1 week of treatment, pain at rest had significantly improved, as measured by a 10-point visual analog scale (VAS) pain score, compared with placebo (weighted mean difference [WMD] 3.08; 95% confidence interval [CI], 2.64–3.52). At the 4-week follow-up, patients taking calcitonin continued to report decreased pain at rest on the VAS pain score when compared with placebo (WMD 4.03; 95% CI, 3.70–4.35).¹

All 5 RCTs examined use of other analgesics. Patients in the calcitonin group had decreased use of paracetamol compared with patients in the placebo groups at 1 week; patients taking calcitonin used about 3 fewer pills per patient in a 24-hour period (WMD 2.72; 95% CI, 2.31–3.13). Subgroup analysis of the 4 RCTs with VAS scores while patients were sitting indicated better pain scores than placebo, whether calcitonin was given intranasally (WMD 2.55; 95% CI, 2.16–2.84), rectally (WMD 2.00; 95% CI, 1.46–2.54), or intramuscularly (WMD 4.00; 95% CI, 3.0–5.0).¹

In a 2002 double-blind RCT, 229 independently living patients older than 65 with acute hip fracture were randomly assigned 200 IU intranasal calcitonin daily or placebo. All patients received surgical intervention and

internal fixation, hemi-endoprosthesis, or total prosthesis. Three months after the operation, mean intensity of pain on VAS was measured and interquartile range (IQR) was recorded as 0 mm (IQR 0.20) in the calcitonin group and 4 mm (IQR 0.35) in the placebo group ($P=.15$).²

Alex Parker, BS
Angelica M. Soberon, MD
José E. Rodríguez, MD
Florida State University
Tallahassee, FL

- Knopp JA, Diner BM, Blitz M, Lyritys GP, Rowe BH. Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. *Osteoporos Int.* 2005; 16(10):1281–1290. [LOE 1a]
- Huusko TM, Karppi P, Kautiainen H, Suominen H, Avikainen V, Sulkava R. Randomized, double-blind, clinically controlled trial of intranasal calcitonin treatment in patients with hip fracture. *Calcif Tissue Int.* 2002; 71(6):478–484. [LOE 1b]

For the initial management of dyspepsia, what strategy is best to prevent recurrent dyspepsia/gastritis?

Evidence-Based Answer

It appears there is little difference in efficacy at 1 year between a *Helicobacter pylori* “test-and-treat” strategy and empiric proton-pump inhibitor (PPI) treatment for initial management of patients with dyspepsia, even if the *H pylori* prevalence rate is as high as 25% to 30%. (SOR **A**, based on a meta-analysis and subsequent randomized controlled trial [RCT].)

A 2008 United Kingdom meta-analysis of 3 RCTs involving 1,547 patients (mean age 42.6 years, 48.6% male) compared a *H pylori* test-and-treat strategy with empiric PPI therapy for the outcome of dyspeptic symptom resolution over 1 year. Dyspepsia was defined more broadly than the Rome III classification as a cluster of symptoms including both epigastric pain and heartburn. One RCT tested patients by *H pylori* serology, and 2 RCTs used the ¹³C urea breath test. The prevalence of *H pylori* ranged from 23% to 29% in the test-and-treat arm of these trials. For the test-and-treat strategy, a 1-week course of PPI-based triple therapy was used for *H pylori*-positive patients. The empiric PPI strategy utilized 4 weeks of a PPI (given twice daily in 1 trial). No significant difference was noted for 12-month symptom reduction (83% symptomatic with test-and-treat vs 84.5% symptomatic with empiric PPI therapy; relative risk [RR]=0.99; 95% confidence interval [CI], 0.95 to 1.03).¹

In a 2008 United Kingdom multicenter, primary care-based RCT, 699 patients (49% male) were randomized to either test-and-treat or empiric PPI treatment. Dyspepsia was defined using the Rome I criteria. Patients with a positive ¹³C urea breath test received 1 week of PPI-based triple therapy followed by daily PPI for 3 weeks. *H pylori* prevalence was 29% in the test-and-treat arm. A repeat ¹³C urea breath test was conducted 3 months after treatment, and the successful eradication rate was 78%. Patients randomized to the PPI strategy received 4 weeks of daily PPI. No significant difference was observed for 12-month symptom reduction between groups (82% symptomatic in the test-and-treat group vs 83% symptomatic in the PPI group; RR=0.99; 95% CI, -5.4 to 7.6).²

Current clinical guidelines published by both the American College of Gastroenterology and the American Gastroenterological Association recommend a test-and-treat strategy for patients <55 years followed by PPI therapy for symptomatic patients. These guidelines note that benefit of the test-and-treat strategy is likely to be reduced if local *H pylori* prevalence is <10% to 20%.^{3,4} The Maastricht III Consensus Report of the European Helicobacter Study Group recommends a test-and-treat strategy for adult patients ≤45 years with persistent dyspepsia, but states that in populations of low *H pylori* prevalence (<20%) the test-and-treat and empiric PPI strategies are equivalent treatment options.⁵

Brent Scroggins, MD
Darrell R. Over, MD, MSc
U of AR for Medical Sciences AHEC
Pine Bluff, AR

- Ford AC, Moayyedi P, Jarbol DE, Logan RF, Delaney BC. Meta-analysis: *Helicobacter pylori* “test and treat” compared with empirical acid suppression for managing dyspepsia. *Aliment Pharmacol Ther.* 2008; 28(5):534–544. [LOE 1a]
- Delaney BC, Qume M, Moayyedi P, et al. *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). *BMJ.* 2008; 336(7645):651–654. [LOE 1b]
- Talley NJ, Vakili N; for the Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. *Am J Gastroenterol.* 2005; 100(10):2324–2337. [LOE 5]
- Talley NJ, Vakili NB, Moayyedi P. American Gastroenterological Association Technical Review on the evaluation of dyspepsia. *Gastroenterology.* 2005; 129(5):1756–1780. [LOE 5]
- Malfertheiner P, Megraud F, O’Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III consensus report. *Gut.* 2007; 56(6):772–781. [LOE 5]

Is antiviral therapy for acute, localized herpes zoster safe and effective?

Evidence-Based Answer

Oral famciclovir, valacyclovir, and acyclovir are all well tolerated and accelerate resolution of pain associated with subacute herpetic neuralgia (SHN) in patients 50 years of age or older (SOR **A**, multiple randomized controlled trials [RCTs]). However, acyclovir was found to have no significant effect in reducing postherpetic neuralgia (PHN) at 4 and 6 months (SOR **A**, based on a high-quality meta-analysis), and evidence is insufficient to determine whether famciclovir or valacyclovir reduce PHN.

Acute herpetic neuralgia is defined as pain within 30 days of rash onset, SHN as pain 30 to 120 days after rash onset, and PHN as pain continuing at least 120 days from rash onset.¹

A Cochrane review of 5 acyclovir and 1 famciclovir RCTs was done to assess their efficacy in preventing PHN. A total of 1,211 patients (69% >50 years old) were included in the review. A subanalysis of acyclovir studies that had data on the presence of pain 1 month after the onset of rash was feasible for 4 RCTs (n=692). It showed that acyclovir (800 mg 5 times daily for 7–14 days), started less than 72 hours after rash onset, significantly lowered the incidence of SHN when compared with placebo (44% vs 53%, respectively; relative risk [RR] 0.83; 95% confidence interval [CI], 0.71–0.96; $P=.01$).²

The multicenter RCT of famciclovir included in the Cochrane review enrolled 419 immunocompetent adults (mean age 50 years) with uncomplicated herpes zoster of less than 72 hours' duration. They were randomized to receive famciclovir 500 mg 3 times daily for 7 days, famciclovir 750 mg 3 times daily for 7 days, or placebo. The median time to resolution of pain was 63 days for the 500-mg famciclovir group, 61 days for the 750-mg famciclovir group, and 119 days for the placebo group (hazard ratio [HR] 1.7; 95% CI, 1.1–2.7).³

In a multicenter comparison trial not included in the Cochrane review, 760 patients (mean age 55.9 years) with herpes zoster of less than 72 hours' duration were randomized to receive either valacyclovir (1,000 mg 3 times daily for 7 days) or acyclovir (800 mg 5 times daily for 7 days). The primary endpoint was the time

to control zoster-associated pain. Valacyclovir was associated with resolution of pain in an average of 40 days, compared with acyclovir, which took 49 days (HR 1.34; 95% CI, 1.12–1.60; $P=.001$).⁴ A key weakness in this study was the lack of a placebo control.

Antiviral medications appear to help in controlling pain when assessed before 120 days. However, the same Cochrane review mentioned earlier focused on the primary outcome of presence of PHN 6 months after the onset of the rash. A meta-analysis of 5 RCTs (n=1,085) comparing acyclovir with placebo, in patients older than 50 years, showed that oral acyclovir was not statistically different from placebo in reducing the incidence of pain at 4 to 6 months after the onset of the rash (RR 1.05; 95% CI, 0.87–1.27; $P=.62$). In terms of valacyclovir and famciclovir, authors concluded not enough studies are available to determine their effect on PHN.²

With respect to their side effects, none of the above-mentioned trials reported any serious effects attributable to the antiviral agents. The most commonly reported adverse events were nausea, vomiting, diarrhea, and headache, and none was statistically significant compared with placebo (RR 1.01; 95% CI, 0.88–1.15).^{2–4}

EBP

Maria Veronica Abello-Poblete, MD
Alan Remde, MD

UMDNJ-RWJ FMPR at Capital Health System
Plainsborough, NJ

1. Arani RB, Song SJ, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: a new statistical approach. *Stat Med.* 2001; 20(16):2429–2439. [LOE 2c]
2. Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev.* 2009; (2):CD006866. [LOE 1a]
3. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Ann Intern Med.* 1995; 123(2):89–96. [LOE 1b]
4. Tyring SK, Beutner KR, Tucker BA, Anderson WC, Crooks RJ. Antiviral therapy for herpes zoster: randomized, controlled trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Arch Fam Med.* 2000; 9(9):863–869. [LOE 1b]

“Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”

—Sackett DL et al. Evidence based medicine:

what it is and what it isn't. *BMJ* 1996; 312:71–72.

What is the efficacy and safety of sinecatechins and imiquimod when treating genital and perianal warts?

Bottom line

Sinecatechins (Veregen®) and imiquimod (Aldara®) produce comparable clearance rates in the treatment of patients with anogenital warts. Itching, the most common local side effect of either agent, is more common with imiquimod. (SOR B, based on a single randomized controlled trial of sinecatechins and systematic reviews of imiquimod.)

Evidence summary

Sinecatechins

In a double-blind, multicenter, parallel-group, vehicle-controlled trial, 502 patients with genital or perianal warts were randomized into 1 of 3 treatment groups for 16 weeks.¹ The groups received sinecatechins 15% ointment (n=196), sinecatechins 10% ointment (n=202), or a placebo vehicle (n=104) to apply 3 times daily. Treatment continued for 16 weeks or until warts healed (whichever came first), and participants were followed for 12 weeks after treatment ended.

The primary endpoint was complete clearance of all warts, which was achieved in 111 patients in the sinecatechins 15% group, 111 in the sinecatechins 10% group, and 35 in the vehicle-only group (57.2%, 56.3%, and 33.7% respectively, $P<.001$; number needed to treat [NNT]=4 for both concentrations). During the 12 weeks after treatment, 6.5% in the 15% sinecatechins group and 8.3% in the 10% sinecatechins group experienced recurrence, compared with 8.8% in the vehicle-only group (no P value was assigned).

The most common adverse events were mild- to moderate-intensity localized skin reactions (87.7% [sinecatechins 15% ointment], 87.3% [sinecatechins 10% ointment], and 72.1% [vehicle only]). Itching, the most predominant severe local reaction, occurred in 14.7% (sinecatechins 15% ointment), 16.1% (sinecatechins 10% ointment), and 3.2% (vehicle only) of participants. Vulvitis, vulvovaginitis, and lymphadenitis occurred in participants using sinecatechins 15% (n=5) and 10% (n=2). Fifteen patients using sinecatechins experienced systemic side effects (infections and infestations), all reported as mild or moderate.

Imiquimod

A systematic review of 6 trials evaluated the safety and efficacy of 5% imiquimod in the treatment of patients with genital warts.² Three (n=254) trials reported a principal outcome of complete clearance without recurrence for 37% (95% confidence interval [CI], 31%–43%; NNT=3) of patients using 5% imiquimod cream 3 times a week, compared with 4% for those receiving placebo. Common adverse events included burning, itching, erythema, and erosion. Of patients using imiquimod, 4 withdrew because of adverse events (relative risk=1.9; 95% CI, 0.4–10; number needed to harm not calculated).

A meta-analysis of 3 trials (n=194) trials compared 5% imiquimod with placebo.³ These studies showed a complete clearance rate of 50.34% among patients using imiquimod (pooled odds ratio relative 11.65; 95% CI, 6.05–22.44; NNT=2.5). Recurrence rates reported in 2 trials (n=61) were 13% and 19%, respectively. Adverse events with imiquimod included itching, erythema, erosion, and burning (38%, 37%, 13%, and 20%, respectively). Five patients withdrew because of adverse events.

Centers for Disease Control recommendations

The Centers for Disease Control recommend the use of either imiquimod 5% cream 3 times daily for up to 16 weeks, or podoflox 0.5% solution or gel applied twice daily for 3 days and then no treatment for 4 days, up to 4 cycles.⁴

EBP

Josephine Schobert, PharmD candidate

Connie Kraus, PharmD

U of WI School of Pharmacy
Madison, WI

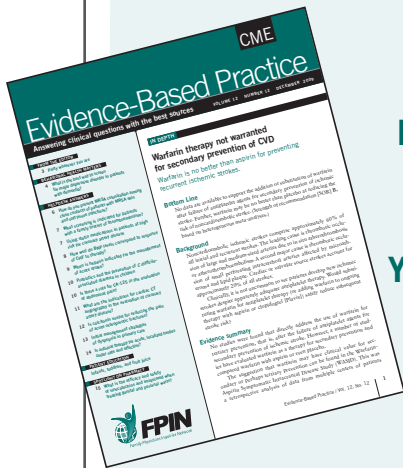
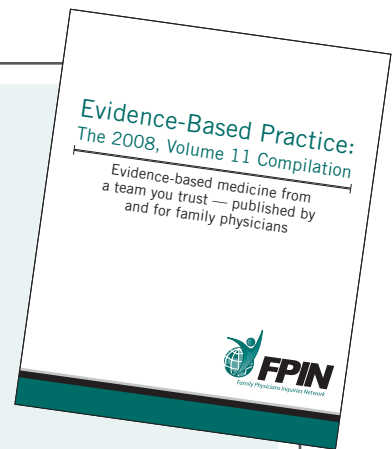
REFERENCES

1. Tatti S, Swinehart JM, Thielert C, Tawfik H, Mescheder A, Beutner KR. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol.* 2008; 111(6):1371–1379. [LOE 1b]
2. Moore RA, Edwards JE, Hopwood J, Hicks D. Imiquimod for the treatment of genital warts: a quantitative systematic review. *BMC Infect Dis.* 2001; 1(3). [LOE 1a]
3. Yan J, Chen SL, Wang HN, Wu TX. Meta-analysis of 5% imiquimod and 0.5% podophyllo-toxin in the treatment of condylomata acuminata. *Dermatology.* 2006; 213(3):218–223. [LOE 1a]
4. Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. HPV infection and genital warts. *MMWR Recomm Rep.* 2006; 55(RR-11):62–67. [LOE 5]

Family Physicians Inquiries Network, Inc.
409 West Vandiver Drive
Building 4, Suite 202
Columbia, MO 65202

Change Service Requested

PRESORTED
STANDARD
U.S. POSTAGE
PAID
LINCOLN, NE
PERMIT # 365



Subscribe or Renew Today!
Place your order for *Evidence-Based Practice* before December 31, 2009, and receive a free copy of our current EBP Compilation!
You can subscribe or renew online at FPIN.org by clicking on the **SUBSCRIBE** button or by calling us at 573-256-2066.

See Insert for 2010 subscription rates.

CONTINUING MEDICAL EDUCATION TEST

Evidence-Based Practice DECEMBER 2009

For each question, please mark the single best answer by checking the appropriate box.

- Which of the following statements is true regarding the use of HMG-CoA reductase inhibitors (statins) in patients at high risk for coronary artery disease (CAD)?
 - a. Treatment with a standard-dose statin regimen is more effective than using intensive-dose therapy to prevent mortality in patients with acute coronary syndrome
 - b. Intensive statin therapy is more effective than standard therapy to reduce mortality and morbidity in patients with diabetes and normal kidney function
 - c. Treatment with statins increases morbidity and mortality in patients with CAD
 - d. The use of intensive lipid-lowering therapy in patients with CAD lowers the risk of myocardial infarction and stroke more than standard-dose therapy
- Meta-analysis data suggest that in the prevention of recurrent noncardioembolic stroke
 - a. Warfarin causes no more significant bleeding than placebo
 - b. Anticoagulation is more effective than antiplatelet therapy
 - c. Warfarin is synergistic with aspirin
 - d. Anticoagulation and placebo have the same mortality rate
- Which of the following is not an effect of heparin use within 14 days of stroke onset?
 - a. An increase in intracranial hemorrhage
 - b. An increase in extracranial hemorrhage
 - c. Increased incidence of pulmonary embolism
 - d. Decreased incidence of recurrent ischemic stroke
- Which set of tests is most valuable for the evaluation of depression in patients with dementia?
 - a. Geriatric Depression Scale
 - b. Cornell Scale for Depression in Dementia
 - c. Nurses Observation Scale for Geriatric Patients
 - d. Even Briefer Assessment Scale for Depression
- Which statement is most accurate regarding the management of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in a community?
 - a. Topical metronidazole is the best medication for the treatment of MRSA colonization
 - b. Good hygiene is recommended to prevent of MRSA colonization
 - c. MRSA colonization is rare and not a major concern in most outbreaks
 - d. Daily chlorhexidine baths by the caretakers of patients with MRSA soft tissue infections effectively prevents colonization by MRSA
- Which probiotic reduced the rate of antibiotic-associated diarrhea in children treated with antibiotics for otitis media or upper respiratory tract infection?
 - a. *Saccharomyces boulardii*
 - b. *Lactobacillus casei*
 - c. *Lactobacillus bulgaricus*
 - d. *Streptococcus thermophilus*
- Genetic testing for patients with a high-risk family history for thromboembolism:
 - a. Should be provided for all first-degree relatives of patients with thrombophilias
 - b. Allows better targeted recommendations for anticoagulant therapy in high-risk situations
 - c. Has no bearing on life and disability insurance of these patients, because there is no evidence that they will definitely manifest the disease
 - d. Is highly cost effective
- Which of the following adverse reactions is most commonly experienced with imiquimod treatment for anogenital warts?
 - a. Erosion
 - b. Erythema
 - c. Itching
 - d. Burning

For 2009, all AAFP members who subscribe to EBP CME are eligible to earn 2 Prescribed Academy credits monthly toward their AAFP membership. Please complete and return the CME activity by March 31, 2010.

This test must be received by March 31, 2010 to be accepted for credit

Answer key: 1. d; 2. d; 3. c; 4. b; 5. b; 6. a; 7. b; 8. c

A maximum of 2 prescribed AAFP credits per month are available to EBP subscribers. For each test submitted, send no money if you have the enhanced EBP subscription with CME upgrade; if you have a regular EBP subscription without CME, include a check for \$15.00 per test submitted, payable to "Family Physicians Inquiries Network".

To ensure proper credit for your CME test, please provide the following information:

Name (Please print) _____ Title (MD, DO, etc) _____ SSN (last 4 digits) _____

Address _____

City _____ State _____

Zip Code _____ Daytime Phone Number _____ Ext. _____

Email address (to notify you of credits earned) _____

Please return your test to Family Physicians Inquiries Network, 409 W. Vandiver Drive, Bldg. #4, Suite 202, Columbia, MO 65202. If you use the attached mailer, be sure to seal and affix proper postage. If you have questions about your CME credits, or to renew or subscribe to EBP, please contact our EBP Project Manager, Genny Jacks, by email at genny@fpin.org or telephone 573-256-2066.

Renew or Subscribe to EBP at fpin.org or call 573-256-2066

CLINICAL INQUIRIES: PATIENT EDUCATION

Information you can trust. Information you can use.

Based on the Clinical Inquiries® by the Family Physicians Inquiries Network:

When is it OK for children to start drinking fruit juice?

Journal of Family Practice, September 2009, Vol. 58, No. 9

Infants, Toddlers, and Fruit Juice

It is exciting to introduce new foods to your infant and watch as they react to new flavors. Infants and toddlers usually love fruit juices and fruit drinks. They often start asking for juice while still nursing or drinking from a baby bottle. But research shows there is reason to be cautious about giving them fruit drinks.

Breastfeeding is still the perfect food for infants. Breastfeeding should continue for the first 6 months, or even 1 year if possible. Drinking fruit juices may sound healthy, but fruit-flavored drinks often contain lots of sugar and very little actual fruit. If your child drinks too much juice he or she might not eat enough foods that contain protein to grow healthy. Studies show fruit juices and other sugary foods can add to weight problems in children. And overweight children often become overweight adults. Drinking fruit drinks from a baby bottle also contributes to cavities in your child's teeth.

If your children drink too many fruit juices and fruit drinks, they can get into a habit of wanting brightly packaged, easy-to-hold sugary drinks. If you buy a lot of juice boxes for your children, they do not get the fiber and vitamins that come from eating natural fruit. Juice drinks also contain corn syrup and other artificial flavorings.

So, what is a parent to do? Remember that breastfeeding is always best. Do not give fruit juice to a child younger than 6 months of age. When you do give juice, it should be 100% fruit juice in a cup, not a bottle. Children 1 to 6 years of age should drink no more than 4 to 6 ounces of 100% fruit juice per day. And children 1 to 3 years old should eat the equivalent of 1 cup of whole fruit a day.

These suggestions will help your child develop an appetite for healthy foods and have a normal weight. These will help your child for years to come. Think whole fruit and not sugary drinks.

For more information

Infant and Toddler Nutrition (MedlinePlus)
<http://www.nlm.nih.gov/medlineplus/infantandtoddlernutrition.html>

The Use and Misuse of Fruit Juice in Pediatrics (American Academy of Pediatrics)
<http://aappolicy.aappublications.org/cgi/content/full/pediatrics;107/5/1210>

Feeding Your 1- to 3-Month-Old, 4- to 7-Month-Old, 8- to 12-Month-Old, 1- to 2-Year-Old (Kids Health from Nemours)
http://kidshealth.org/parent/nutrition_fit/