Does head CT assist in the diagnosis of an adult with syncope?

Evidence-based answer

The *routine* use of head computed tomography (CT) does not assist in the diagnosis of neurologically intact adults with syncope. However, in syncope patients with neurological symptoms or abnormal neurological examination results, head CT does provide important diagnostic information and should be done (SOR: B, cohort and chart review studies).

Evidence summary

A 2010 prospective cohort study evaluated 292 consecutive adults (mean age 62 years; range 32–93 years) presenting to the emergency department (ED) with transient loss of consciousness (LOC) over a 13-month period. The goal was to determine the usefulness of head CT as a routine diagnostic test in syncope. Thirty-eight patients (13%) were excluded for conditions causing LOC other than syncope, including history of trauma, known brain tumor, epilepsy, psychiatric illnesses, intoxication, hypoglycemia, or hyperventilation. The remaining 254 patients underwent examination by a neurologist and head CT.

Two hundred three patients (80%) had normal neurological exam results and a normal head CT, defined as no focal brain lesion, no shift of midline structures, no intra- or extra-axial brain hemorrhage, and normal gray-white matter differentiation. Fifty-one patients had an abnormal head CT, of whom 10 patients had findings (2 brain tumors, 3 intra-parenchymal bleeds, 1 subarachnoid hemorrhage, 1 ischemic stroke) that could explain a syncopal episode. All 10 also had abnormal neurological examination results. No patient with a normal neurological examination result had head CT findings related to syncope.

A 2007 prospective cohort study evaluated 293 consecutive patients presenting to the ED with syncope to determine the yield of routine head CT in the evaluation of syncope. Patients were ≥18 years old with syncope defined as sudden, transient LOC resulting in loss of postural tone and unresponsiveness with spontaneous recovery. Patients were excluded if they experienced prolonged altered mental status, alcohol- or drug-related LOC, seizures, hypoglycemia, or LOC due to trauma.

Head CT was performed on 113 patients (39%), of whom 5 (4%) were abnormal (2 subarachnoid hemorrhages, 2 cerebral hemorrhages,
TABLE

Chart reviews of CT findings in patients seen in an emergency department setting after syncope

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients who had CT</th>
<th>Number of CTs with any abnormality</th>
<th>CT abnormalities identifying etiology of syncope</th>
<th>Patients with normal exam and abnormal CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pires et al (N=649)</td>
<td>283</td>
<td>31</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Vanbrabant et al (N=117)</td>
<td>41</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Goyal et al (N=202)</td>
<td>117</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

and 1 ischemic stroke). Among the 5 patients with an abnormal head CT, 1 displayed focal neurological findings, 2 had new headaches, and 2 had no new neurological findings but had signs of significant head trauma sustained after LOC suggesting the intracranial hemorrhages could have been caused by trauma after LOC. All patients with abnormal head CTs were older than 65 years. Among 180 patients who did not have a head CT, none developed new neurological disease during the 30-day follow-up.

Three retrospective chart reviews add further data and are summarized in the TABLE. A 2001 retrospective chart review identified 649 consecutive adults (>18 years old) hospitalized with a principal diagnosis of syncope for the purpose of assessing diagnostic patterns in the evaluation of syncope.

A 2011 retrospective chart review identified 117 consecutive patients (mean age 57 years; range 6–93 years) presenting to the ED with syncope to determine the diagnostic yield of various diagnostic procedures, including head CT. Twenty-nine patients were excluded due to incomplete or inaccurate registration (n=3), lack of data (n=1), seizures (n=2), or undefined “presyncopal event” (n=23).

A 2006 retrospective chart review of all adults (≥18 years old) presenting to the ED with syncope who received a head CT (n=202) sought to determine if head CT aided in the diagnostic evaluation of syncope. Patients were excluded (n=85) if they had alternative indications other than syncope for undergoing a head CT, including history of trauma, seizures, and altered mental status including intoxication and neurological deficits on initial evaluation.

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REFERENCES
Getting out the umbrella

The latter months of the year are typically drizzly in Seattle and everyone who has business outside dresses in Gor-Tex or carries an umbrella. The rain in Seattle is generally rather light (often described as like standing in a car wash), but it is persistent, with Pacific squalls coming through every 1 to 3 days.

When you combine the high latitude, the cloud cover, and the cool weather, those of us who live in this area don’t generate much vitamin D (or tan lines for that matter). Heaven help the Seattleite who happens to be lactose intolerant, because the milk supply really is the only reliable vitamin D source. It’s local medical lore that “everyone” around here is vitamin D deficient in the winter and lots of people take supplements.

Vitamin D supplementation certainly has its supporters. Historically, vitamin D deficiency has been linked to metabolic bone diseases, fractures, falls, muscle strength, cancer rates, cardiovascular disease, infections, autoimmune diseases, and all-cause mortality, among other things. Sometimes it sounds like vitamin D is akin to a veritable fountain of youth.

Unfortunately, when something sounds too good to be true, it probably is. Getting out another kind of umbrella—an umbrella meta-analysis—a group of researchers reviewed 74 meta-analyses of observational studies and 87 meta-analyses of RCTs of vitamin D supplementation covering 137 different clinical outcomes.1 When all the numbers had been shaken out, the authors found that “highly convincing evidence of a clear role of vitamin D with highly significant results in both randomized and observational evidence does not exist for any outcome.”

The authors did concede there was a “probable” connection between vitamin D and kids’ dental health, birth weights, and bone health in chronic kidney disease. But the effects on cardiovascular health and nonvertebral fractures were only deemed “suggestive.” The vast majority of popular associations were rated as having insufficient evidence to judge.

So maybe the extra vitamin D isn’t making most of our lives any better. But on some dark days, all we really want is sunshine in a pill.

Jon O. Neher, MD

REFERENCE

1. Theodoratou E, Tzoulaki I, Zgaga L, Ionannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014; 348:g2035.
**No benefit to partial medial meniscectomy in patients without osteoarthritis**


This multicenter double-blind RCT of 146 patients aged 35–65 years (mean age 52) compared partial medial meniscectomy with sham meniscectomy. All patients had at least 3 months of knee pain that had failed conservative treatment and a clinically suspected medial meniscus tear confirmed by MRI. Patients were excluded if they had locking of the knee, osteoarthritis confirmed clinically or radiologically, recent fracture, previous knee surgery, an unstable knee, or onset of pain with trauma that caused a fall (not just twisting or bending).

All 146 patients had diagnostic arthroscopy and were then immediately randomized to real or sham surgery. At 12 months, pain and function was evaluated on an 11-point scale. The Lysholm score (100-point scale) was used to evaluate activities of daily living and the Western Ontario Meniscal Evaluation Tool (WOMET) score was used to evaluate quality of life (100-point scale).

Although both groups improved over the year of the study, no significant difference was noted between the 2 groups when comparing change from baseline. Knee pain score between-group difference was –0.1 (95% CI, –0.9 to 0.7), Lysholm between-group difference was –1.6 (95% CI, –7.2 to 4), and WOMET between-group difference was –2.5 (95% CI, –9.2 to 4.1).

**Bottom line:** This study calls into question the strategy of ordering MRIs on such patients and referring them to surgery.

| Relevant | Yes | Medical care setting | Yes |
|------------------------|------------------------|------------------------|
| Valid | Yes | Implementable | Yes |
| Change in practice | Yes | Clinically meaningful | Yes |

**Intramuscular betamethasone for acute gout may reduce pain faster than oral diclofenac sodium**


This open-label randomized trial compared 1 dose of intramuscular compound betamethasone (n=30) with oral diclofenac sodium twice daily for 7 days (n=30) for treatment of acute gouty arthritis.

The percentage of patients reporting severe pain at baseline compared with 4 hours after starting treatment was reduced from 90% to 57% in the betamethasone group and from 93% to 73% in the diclofenac group (P<.05 for difference in response).

Patient and physician report of a positive global response to therapy was higher with the compound betamethasone than with diclofenac at day 3 (10 vs 3 patients reporting 0 on the pain scale; P=.013 and 10 vs 2 patients with very good response; P<.05). In addition, physicians observed less joint swelling (2 vs 7 patients; P<.05) and less tenderness (2 vs 8 patients; P<.05) on day 3 with betamethasone compared with diclofenac.

No significant differences were noted in outcomes between the 2 treatments on day 7. There were more adverse events, including gastrointestinal effects, in the diclofenac sodium group than in the betamethasone group (6 vs 3).

**Bottom line:** Intramuscular compound betamethasone for acute gouty arthritis led to less pain 3 days after treatment compared with oral diclofenac, but lack of blinding and concealed allocation keep us from recommending this as a practice change at this time.

| Relevant | Yes | Medical care setting | Yes |
|------------------------|------------------------|------------------------|
| Valid | No | Implementable | Yes |
| Change in practice | Yes | Clinically meaningful | Yes |

Review and Summary Author: Jennifer Bello, MD, NorthShore University Health System, Chicago, IL

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Additional information can be found at: [www.fpin.org/purlsfaqs](http://www.fpin.org/purlsfaqs)
**Diving for PURLs**

**Naltrexone and acamprosate can help prevent alcohol relapse**


This meta-analysis included 95 RCTs including 22 placebo-controlled trials of acamprosate and 44 of naltrexone. The trials lasted from 12 to 52 weeks with the mean age of participants around 40 years. Participants were primarily recruited from the inpatient setting and enrolled after detoxification or 3 days of sobriety. Most studies also included psychosocial interventions such as counselling or attendance at Alcoholics Anonymous meetings for the intervention and control groups.

To prevent 1 patient from relapsing to any drinking, 12 patients needed to be treated with acamprosate versus placebo (NNT=12; 95% CI, 8–26). The NNT for oral naltrexone was 20 (95% CI, 11–500). Meta-analyses of trials comparing acamprosate with naltrexone found no statistically significant difference between them for return to any drinking (risk difference [RD] 2%; 95% CI, −0.03 to 0.08) or heavy drinking (RD 1%; 95% CI, −0.05 to 0.06). Subgroup analysis of acamprosate trials showed that trials with a larger effect size were more prone to bias. For naltrexone the NNH for withdrawal from trials due to adverse events was 48 (95% CI, 30–112). The risk was not significantly increased for acamprosate.

| Relevant | Yes | Medical care setting | Yes |
| Valid | Yes | Implementable | Yes |
| Change in practice | Yes | Clinically meaningful | Yes |

**Bottom line**: Both acamprosate and oral naltrexone were associated with reduction in risk of return to drinking.

Review and Summary Author: Anne Mounsey, MD, Department of Family Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

**Fluoroquinolones for children?**


This cohort study compared the rate of musculoskeletal adverse events (MSAE) among children (mean age 2.9 years) at high risk for MSAEs who received either levofloxacin (n=124) or a comparator antibiotic (n=83).

Children were considered at high risk if they exhibited poor growth or an MSAE (eg, abnormal bone growth, or related signs or symptoms) during an initial 12-month follow-up study from a multicenter RCT on the use of levofloxacin.

They were then followed annually for 5 years to assess the primary outcome of protocol-defined musculoskeletal disorders (PDMSD), including tendinopathies, arthritis, or arthralgias. Forty-nine percent of the children were lost to follow-up in each group.

After 5 years, 1 child in each group had a PDMSD possibly related to the levofloxacin.

| Relevant | Yes | Medical care setting | Yes |
| Valid | No | Implementable | Yes |
| Change in practice | Yes | Clinically meaningful | Yes |

**Bottom line**: Levofloxacin is unlikely to cause serious MSAE in children. Still, a larger study would help substantiate the observed low frequency of adverse events among children receiving levofloxacin.

Review and Summary Author: Kate Rowland, MD, Department of Family Medicine, The University of Chicago, Chicago, IL

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Evidence-Based Practice / Vol. 17, No. 12
Are behavioral therapies effective for ADHD?

Bottom line
Cognitive training and behavioral interventions are not effective for attention deficit hyperactivity disorder (ADHD) (SOR: A, systematic review). Neurofeedback may be an effective intervention (SOR: C, inconsistent meta-analysis and recent RCT). The use of weighted vests may provide some improvement in ADHD symptoms (SOR: B, single RCT).

Evidence summary
A 2013 systematic review and meta-analysis of 54 RCTs evaluated various nonpharmacologic interventions for the treatment of ADHD, including 6 studies on cognitive training (n=126 treatment, n=123 control), 8 studies involving neurofeedback (n=160 treatment, n=13 control), and 15 studies of behavioral intervention (n=549 treatment, n=492 control). Most of the studies were rated as fair to poor, with 5 studies rated as good or excellent. They evaluated pre- to post-treatment change in ADHD symptom severity on a variety of ADHD-specific symptom scales that varied by study. Authors performed 2 different analyses—1 using the most proximal assessment (defined as the rater closest to the therapeutic setting) and the other a probably blinded assessment (defined as an individual likely to be blind to treatment), with the latter being more stringent in an attempt to reduce the bias.

The most proximal assessment showed improvements in ADHD symptoms with cognitive training (standardized mean difference [SMD] 0.64; 95% CI, 0.33–0.95; P=.0001), neurofeedback (SMD 0.59; 95% CI, 0.31–0.87; P=.0001), and behavioral interventions (SMD 0.40; 95% CI, 0.20–0.60; P=.0001). The probably blinded assessment analysis showed no significant improvements in the cognitive training (SMD 0.24; 95% CI, −0.24 to 0.72; P=.34), neurofeedback (SMD 0.29; 95% CI, −0.02 to 0.61; P=.07), or behavioral interventions (SMD 0.02; 95% CI, −0.30 to 0.34; P=.92).1

A 2014 RCT of 104 children aged 7 to 11 years evaluated the effectiveness of an in-school neurofeedback intervention compared with both cognitive training and control.2 Outcomes included changes from baseline to 6-month follow-up in ADHD symptoms measured with the Conners 3-Parent Assessment Report (Conners 3-P), the Behavior Rating Inventory of Executive Function Parent Form (BRIEF), a classroom observation, and changes to ADHD medication dosages.

Neurofeedback showed statistically significant improvements in all Conners 3-P and BRIEF subscales compared with control, with neurofeedback effect sizes ranging from −0.21 to −0.34 on the different subscales and control effect sizes of −0.12 to 0.08 (P<.05). Neurofeedback also showed significant improvements in 6 Conners 3-P and 6 BRIEF subscales compared with cognitive training, which had effect sizes ranging from −0.01 to −0.08 (P<.05).3

A 2014 randomized crossover study of 110 children diagnosed with ADHD evaluated the efficacy of weighted vests.3 Children were evaluated at 2 points in time using the Conners Continuous Performance Test II (CPT II) and by video recording for on-task behavior. Participants were randomized to wearing a weighted vest at either the first or second assessment.

The weighted vest group showed significant improvements on the CPT II in omission errors, with a mean number of omission errors of 52.6 in the control group and 41.7 in the weighted vest group (P=.002). Mean correct response times were 528 ms for control and 502 ms for weighted vest (P=.002), and response time variability was 22.78 ms for control and 18.66 for weighted vest (P<.001). No significant improvement was noted for commission errors, with a mean of 23.3 for control and 23.9 in the weighted vest condition (P=.287). No improvement was noted in vocalizations, with a mean number of 5.49 in the control group and 4.82 in the weighted vest group (P=.433).3

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REFERENCES
What is the best evaluation for angioedema and urticaria?

Evidence-Based Answer
Evidence is insufficient to recommend any particular stepwise workup for angioedema and urticaria, as even with significant testing the etiology is idiopathic in up to 82% of cases. Consensus opinion recommends being guided by a thorough history and physical examination (SOR: C, nonconsecutive observational studies and consensus opinion).

A prospective observational trial done in Italy investigated the etiology of urticaria and angioedema in 562 patients. Researchers used a detailed history and physical to guide their laboratory evaluation of each patient. Some of the laboratory tests included urinalysis, complement levels, thyroid studies, autoimmune tests, serum protein electrophoresis, studies for infection, gastroscopy, biopsy, and skin prick testing. In some cases, withdrawal of a suspected offending environmental agent with subsequent in vivo and in vitro testing was performed to confirm the etiology.

Excluding the patients who had a classic physical urticaria (ie, cold urticaria), 82% of the remaining 482 patients’ cases were classified as idiopathic. These authors recommended being guided by the history and physical examination.

In another prospective observational trial investigating the etiology of angioedema without urticaria, investigators subjected 776 patients to the same battery of tests. Each patient underwent a detailed history and physical examination and the following laboratory tests: complete blood count, protein electrophoresis, erythrosedimentation rate, examination of stool for ova and parasites, pharyngeal and urine culture, sinus and dental radiography, several autoimmune tests, and complement parameters. Additional testing was based on pertinent clinical findings in some of the cases.

The following main causes of angioedema were found in this study: idiopathic (38%), C1 esterase inhibitor deficiency (25%), substances from food/drug/environment (16%), and angiotensin-converting enzyme inhibitor medications (11%). The authors recommended that, if no causative agent was obvious from the history and physical examination, a C1 esterase inhibitor antigen and C4 antigen level should be measured (particularly because antihistamines and steroids are ineffective for treating C1 esterase inhibitor deficiency). These authors also emphasized the importance of a detailed history and physical examination.

The consensus recommendation in the 2013 urticaria guidelines used by the European Union of Medical Specialties noted that while a few prospective observational studies looked at the distribution of etiologies, no blinded trials evaluated the validity and cost-effectiveness of laboratory testing.

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2. Zingale LC, et al. CMAJ. 2006; 175(9):1065–1070. [STEP 3]

Does the Mediterranean style diet decrease the risk of myocardial infarction, stroke, or death in patients at risk of cardiovascular disease?

Evidence-Based Answer
Probably. The Mediterranean style diet (MSD) is associated with a lower risk of stroke, death from cardiovascular disease, and overall mortality in patients at risk of cardiovascular disease (SOR: B, individual RCT and meta-analysis of cohort studies with mixed populations of risk).

A 2013 RCT of more than 7,400 patients (59% female), 55 to 80 years old with either type 2 diabetes or at least 3 cardiovascular risk factors (smoking, hypertension, elevated low-density lipoproteins, low high-density lipoproteins, overweight or obesity, or a family history of early cardiovascular disease) studied MSD dietary groups supplemented with extra-virgin olive oil or nuts compared with a control group encouraged to eat a low-fat diet. After an average follow-up time of 4.8 years, the study was stopped early based on statistically significant reductions in documented endpoints (myocardial infarction, stroke, and cardiovascular-related death) in the study groups compared with the control group (nut HR 0.70; 95% CI, 0.53–0.94; extra-virgin olive oil HR 0.70; 95% CI, 0.53–0.91).
A 2010 meta-analysis included 13 cohort trials (N=61 to 380,296) assessing the correlation between cardiovascular events and mortality with adherence to the MSD over a period of 4 to 20 years. A scaled scoring system quantified participants’ level of adherence to the MSD based on specific dietary components. One point each was earned for consuming more than median amounts of legumes, fish, cereals, olive oil, fresh fruits, vegetables, nuts, and red wine as well as less than median amounts of red meat and/or dairy. Each 2-point increase in adherence score was associated with a reduced risk of cardiovascular events or mortality (RR 0.90; 95% CI, 0.87–0.93) as well as a reduction in overall mortality (RR 0.92; 95% CI, 0.90–0.94) compared with lower adherence groups. Of note, 7 studies exclusively included participants older than 50 years, 5 studies did not exclude participants with a previous cardiovascular event, and only 1 study excluded smokers, thereby representing mixed populations of individuals both with and without cardiovascular risk factors.

A 2007 prospective cohort trial and part of the above meta-analysis followed nearly 400,000 US men and women for 5 years assessing adherence to an MSD and associations with various health outcomes. Patients were placed into “low” (0–3 points) or “high” (6–9 points) adherence groups based on the scoring system described in the above meta-analysis. Although decreased mortality favored all groups conforming to an MSD, greater benefits were noted in those who were lean and smokers (TABLE).

### TABLE

<table>
<thead>
<tr>
<th>Population</th>
<th>Multivariate HR* for mortality</th>
<th>95% CI</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.79</td>
<td>0.76–0.83</td>
<td>214,284</td>
</tr>
<tr>
<td>Men, CVD</td>
<td>0.78</td>
<td>0.69–0.87</td>
<td>1,473</td>
</tr>
<tr>
<td>Male smoker (normal BMI)</td>
<td>0.54</td>
<td>0.50–0.59</td>
<td>2,637</td>
</tr>
<tr>
<td>Male smoker (obese)</td>
<td>0.80</td>
<td>0.72–0.89</td>
<td>1,787</td>
</tr>
<tr>
<td>Male nonsmoker (normal BMI)</td>
<td>0.82</td>
<td>0.70–0.96</td>
<td>703</td>
</tr>
<tr>
<td>Male nonsmoker (obese)</td>
<td>0.92</td>
<td>0.76–1.1</td>
<td>479</td>
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<tr>
<td>Women</td>
<td>0.80</td>
<td>0.75–0.85</td>
<td>166,012</td>
</tr>
<tr>
<td>Women, CVD</td>
<td>0.81</td>
<td>0.68–0.97</td>
<td>626</td>
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<tr>
<td>Female nonsmoker (normal BMI)</td>
<td>0.77</td>
<td>0.65–0.90</td>
<td>663</td>
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<tr>
<td>Female nonsmoker (obese)</td>
<td>0.89</td>
<td>0.72–1.1</td>
<td>469</td>
</tr>
<tr>
<td>Female smoker (normal BMI)</td>
<td>0.59</td>
<td>0.53–0.66</td>
<td>1,726</td>
</tr>
<tr>
<td>Female smoker (obese)</td>
<td>0.74</td>
<td>0.62–0.88</td>
<td>720</td>
</tr>
</tbody>
</table>

Values listed are for all-cause mortality unless otherwise specified.

*High adherence group (6–9 points) compared with low adherence group (0–3 points).

BMI=body mass index; CVD=cardiovascular disease; HR=hazard ratio; MSD=Mediterranean style diet.

Should patients with elevated CRP levels and no other risk factors be started on a statin?

**Evidence-Based Answer**

The answer is unclear. Although treating patients with an elevated C-reactive protein (CRP) likely reduces adverse cardiovascular (CV) outcomes, patients with elevated CRPs often have other CV risk factors (SOR: B, RCT). The US Preventive Services Task Force guidelines state that evidence that changes in CRP level lead to primary prevention of CV disease is inconclusive.

A double-blinded placebo-controlled RCT examined the effects of 20 mg rosuvastatin therapy on nearly 18,000 healthy men >50 years old and women >60 years old with no history of CV disease, low-density lipoprotein (LDL) <130 mg/dL, and a CRP level ≥2 mg/L. This trial was described as “primary prevention”; however, half of the patients had known risk factors such as Framingham scores with a >10% 10-year CV risk, metabolic syndrome (41%), tobacco use (16%), and a family history of premature heart disease (12%). Patients with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded. The primary endpoint was the incidence of major vascular events (nonfatal myocardial infarction, nonfatal stroke, arterial...
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revascularization, hospitalization for unstable angina, or CV mortality). Secondary endpoints were major vascular events, venous thromboembolism, and all-cause mortality.

After a median follow-up of 1.9 years, the rate of the combined primary endpoint of CV disease was reduced from 1.36 (placebo) to 0.77 (rosuvastatin) per 100 person-years (HR 0.56; 95% CI, 0.46–0.69; NNT=81 for 1.9 years). Patients who achieved LDL cholesterol <70 mg/dL and CRP <1 mg/L had a lower risk in major vascular events (HR 0.21; 95% CI, 0.09–0.52). The calculated 5-year NNT to prevent the primary endpoint was 25 and the 5-year NNT for myocardial infarction, stroke, or total mortality was 32.¹

In the reviews conducted for the US Preventive Services Task Force, the evidence that changes in CRP level directly contributes to primary prevention of coronary heart disease events was deemed inconclusive.²

Are diuretics effective for idiopathic lymphedema?

Evidence-Based Answer
Long-term use of diuretics for treatment of lymphedema or for treatment of the later stages of lymphedema is probably ineffective and has an unacceptable adverse effect profile (SOR: C, expert opinion). The short-term use of diuretics in the early stages of lymphedema may be useful if other comorbid conditions causing edema are present (SOR: C, expert opinion).

An older, double-blind crossover study of 22 women evaluated the efficacy of chlorothiazide 500 mg twice daily 5 days a week and potassium chloride 1 g twice daily compared with placebo and potassium chloride 1 g twice daily for the treatment of primary lymphedema.¹ Women were excluded if they had hepatic, renal, or cardiovascular disease. Patients were placed in either the placebo or treatment group for the initial 14 weeks then crossed over to the other group for another 14 weeks.

After completion of the initial 28 weeks, 20 patients were placed on hydrochlorothiazide 50 mg BID 3 times a week with potassium supplements and were followed from 1 to 8 months.

A significant change was found in patients’ subjective assessment, reduction in limb circumference, and reduction in body weight when taking diuretics (data were presented only graphically). No significant difference in actual limb volume was found. Of the 20 patients given hydrochlorothiazide for a 1- to 8-month follow-up period, 13 had no improvement to marginal improvement after the original trial. Patients who seemed to benefit from diuretics during the trial appeared to maintain their improvements. Data were reported subjectively.¹

According to the 2013 consensus statement of the International Society of Lymphology, diuretics are of minimal to no use in the treatment of lymphedema.² The authors stated the long-term use of diuretics and the use of diuretics in the later stages of lymphedema were not particularly effective and carried the risk of electrolyte and fluid imbalance. Short-term use of diuretics was seen as possibly appropriate if comorbid conditions or complications (eg, ascites) amenable to diuretic therapy were present in the early stages. Short- and long-term uses were not defined.

A 2011 management and treatment consensus guideline in the European Journal of Vascular Medicine recommended against the use of diuretics because of the adverse effect profile.³ Diuretics could increase the concentration of cellular debris in the extracellular space, which in turn may accelerate the permanent fibrotic changes characteristic of lymphedema.

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Evidence-Based Practice learning objectives
1. To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.
2. To understand how groundbreaking research is changing the practice of family medicine.
3. To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.
For pregnant patients who smoke, is nicotine replacement therapy more effective than counseling or no intervention for achieving successful smoking cessation?

Evidence-Based Answer
In pregnant women, nicotine replacement therapy (NRT) produces cessation rates similar to behavioral therapies (SOR: B, systematic review and heterogeneous RCT). NRT may be somewhat more effective in a combination form, such as patch plus a faster-acting product (SOR: B, observational trial). However, nicotine products are category D in pregnancy and guidelines recommend person-to-person psychosocial interventions (SOR: A, evidence-based guideline).

A 2009 Cochrane review of 72 RCTs involving more than 25,000 pregnant women assessed the effects of smoking cessation interventions during pregnancy on smoking behavior and perinatal health outcomes. Interventions included cognitive behavioral therapy (CBT), stage of change, fetal health feedback, and pharmacotherapy (NRT, bupropion).

Compared with usual care, all interventions combined significantly reduced continued smoking in late pregnancy (65 trials, risk ratio [RR] 0.94; 95% CI, 0.93–0.96). In subgroup analyses, NRT was better than usual care (5 trials, RR 0.95; 95% CI, 0.92–0.98), with an effect comparable to CBT (31 trials, RR 0.95; 95% CI, 0.93–0.97) and stage of change (11 trials, RR 0.99; 95% CI, 0.97–1.0). No significant differences were noted in birth outcomes between NRT and usual care.

A 2012 Cochrane review (6 RCTs, N=1,745) examined the efficacy and safety of NRT during pregnancy. For all trials, the intervention combined NRT plus behavioral support and was compared with behavioral support alone or behavioral support plus a placebo. Biological measures were used to validate smoking outcomes. NRT did not result in a significant difference in smoking cessation during pregnancy (RR 1.3; 95% CI, 0.93–1.9).

A 2013 correlational study (N=3,880) examined the dosing effect of NRT during pregnancy. The study compared single-form NRT, combination NRT (patch plus faster-acting nicotine product, ie, gum, lozenge, or inhaler), and no medication. Patients were contacted 4 weeks after the designated quit date. Abstinence was defined as a self-report of not smoking for at least 2 weeks and an expired air carbon monoxide concentration of less than 10 parts per million.

Compared with no medication, the odds for abstinence at 4 weeks were significantly greater with combination NRT (OR 1.9; 95% CI, 1.1–3.3) but not single NRT (OR 1.1; 95% CI, 0.60–1.9). In a sensitivity analysis of completed cases, combination NRT had a significant benefit over no medication (OR 2.1; 95% CI, 1.6–2.9), whereas single NRT showed no significant benefit (OR 1.2; 95% CI, 0.8–1.7).

All forms of nicotine are considered to be pregnancy category D by the US FDA during all trimesters of pregnancy. The US Department of Health and Human Services Clinical Practice Guidelines recommends offering person-to-person psychosocial interventions to pregnant smokers that exceed minimal advice to quit.

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What causes delayed gastric emptying (gastroparesis) besides diabetes?

Evidence-Based Answer
Idiopathic causes are the most common etiology of gastroparesis. Whereas diabetes is the next most common etiology of gastroparesis in adults, drugs are the next most common etiology of gastroparesis in children, followed by postsurgical causes in both adults and children. Less common etiologies include scleroderma, viral illness, Parkinson’s disease, and autoimmune disease (SOR: C, retrospective trials).

Gastroparesis is a syndrome confirmed by the presence of symptomatic delayed gastric emptying in the absence of mechanical obstruction. Symptoms of gastroparesis include nausea, vomiting, early satiety, postprandial fullness, abdominal pain, and bloating.

One retrospective hospital chart review trial aimed to describe the demography and clinical characteristics...
of 146 hospitalized patients (aged 15–76 years), who were diagnosed with gastroparesis and referred for consultation to one of the study’s authors over a 6-year span. It was not clear that these patients were hospitalized primarily due to gastroparesis.

The etiologies of gastroparesis were classified as follows: 36% idiopathic, 29% diabetic, 13% postgastric surgery, 7.5% Parkinson’s disease, 4.8% collagen vascular disorders, 4.1% intestinal pseudoobstruction, and 6% miscellaneous causes. This classification did not allow for the possibility that a gastroparesis patient may have had more than 1 etiology. Idiopathic gastroparesis was, in turn, classified according to associated, not causal, and clinical states such as gastroesophageal reflux disease (19%), depression (23%), recent viral illness (23%), and recent cholecystectomy (7.7%). The study’s authors noted a history of physical and sexual abuse in 62% of the female patients with idiopathic gastroparesis. A limitation of this study was the selection bias of primarily adult patients referred to just 1 of the study’s authors at a tertiary-care university center.

Another retrospective observational trial focused on the demography and clinical characteristics of 239 pediatric patients (aged 0–21 years) diagnosed with gastroparesis over a 6-year span. Patients were part of a university outpatient pediatric gastroenterology practice. This study’s analysis allowed for the possibility of multiple etiologies of gastroparesis per patient, which were as follows: 70% idiopathic, 18% drugs (narcotics, anticholinergics, beta-adrenergics, calcium channel blockers, glucagon, marijuana, alcohol, and tobacco), 13% postsurgical, 5% postviral, 4% diabetic, 3.3% other endocrine, 2% rheumatologic, 1.6% metabolic, and 6.3% miscellaneous. Surgeries causing gastroparesis were specified as fundoplication, vagotomy, Whipple procedure, and heart/lung transplant. A preceding viral illness was classified as an etiology of gastroparesis, not just an associated clinical state. Similar to the previous study, patients selected for this study had been referred to an academic medical center.

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Evidence-Based Answer
Are leukotriene receptor antagonists beneficial for the management of adults with asthma exacerbations?

In adults with asthma exacerbations due to viral upper respiratory tract infections, adding leukotriene receptor antagonists (LTRA) to usual care does not decrease hospitalizations (SOR: A, meta-analysis). Adding an LTRA might reduce the length of therapy (SOR: C, small RCT).

A Cochrane review examined 8 RCTs (with 1,470 adults and 470 children) to evaluate the effectiveness of adding an LTRA to standard therapy for asthma exacerbations ($\beta_2$-agonists, systemic corticosteroids, and oxygen). No significant difference was noted in risk of hospitalization in children (3 trials, N=194 children; risk ratio [RR] 0.86; 95% CI, 0.21–3.5). Data comparison for adult hospitalizations was not available. One trial of 641 adults demonstrated a significant difference in FEV$_1$ improvement with oral LTRA versus standard therapy (mean difference [MD] 0.08 L; 95% CI, 0.01–0.14). No significant difference was noted in hospitalizations when intravenous LTRA was compared with standard therapy (3 trials, N=772 adults; RR 0.78; 95% CI, 0.57–1.1).

A 2012 RCT in Japan evaluated the effect of adding pranlukast, an LTRA, to the standard therapy of short-acting $\beta_2$-agonists (SABA) and oral prednisolone (PSL) on the length of treatment required to return the patient to baseline function in 23 adults with an asthma exacerbation from a viral infection (confirmed respiratory syncytial virus or influenza). All patients had been previously controlled with inhaled corticosteroids. In the LTRA+PSL arm the duration of therapy was significantly shorter than in the PSL-alone arm (7.3 vs 14 days, respectively; $P=.03$). However, the overall time to elimination of asthma symptoms was not significantly different between the 2 arms (PSL vs PSL + LTRA: 16 vs 11 days; $P=.06$). Limitations in this study included small sample size and lack of a placebo-controlled arm.

For acute asthma exacerbations, the 2007 National Heart, Blood, and Lung Institute (NHBLI) guidelines recommend administration of inhaled SABA with or without ipratropium and systemic corticosteroids. Adjunct therapies that may be considered to avoid...
intubation include magnesium sulfate and heliox, or interventions based on expert opinion such as epinephrine, long-acting β₂-agonists (LABA), and an LTRA.³

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How effective are lower extremity compression devices for reducing DVT risk after a stroke?

Evidence-Based Answer
Graduated compression stockings (GCS) are no more effective than best medical management (such as anticoagulation therapy, early mobilization and hydration) at reducing deep vein thrombosis (DVT) risk after a stroke (SOR: A, meta-analysis). However, thigh-length intermittent pneumatic compression devices (IPC) using sequential circumferential compression at a frequency determined by venous refill time may decrease the risk of DVT after stroke (SOR: B, inconsistent results from meta-analysis of RCTs and single larger RCT).

A 2010 Cochrane review of 4 RCTs examined the effectiveness of GCS or IPC for the prevention of DVT in 2,792 patients with acute stroke.¹ GCS or IPC was compared with best medical treatment, defined as antiplatelet or anticoagulant therapy, early mobilization, and hydration.

When combined, GCS and IPC did not significantly decrease DVT risk (OR 0.85; 95% CI, 0.7–1.0). Specifically, no difference was noted in DVT risk with either GCS (2 trials, N=2,615; OR 0.88; 95% CI, 0.72–1.1) or IPC (2 trials, N=177; OR 0.45; 95% CI, 0.19–1.1) compared with best medical management; however, the latter study was small and had a wide confidence interval. GCS use caused skin ulceration, breaks, blisters, and necrosis on the legs (OR 3.5; 95% CI, 2.2–5.4).¹

A 2013 RCT examined the effectiveness of IPC to reduce the risk of DVT in 2,876 patients with acute stroke.² Patients who were immobile and admitted within 3 days of stroke onset were randomized to IPC or medical management. The IPC devices were thigh-length sleeves that used sequential circumferential compression at a frequency determined by the venous refill time of the individual patient. DVT screening was done with duplex ultrasound at 7 to 10 days and 25 to 30 days, and a follow-up questionnaire was sent at 6 months. This study found that, compared with medical management, IPC decreased the risk of DVT at the 30-day mark (OR 0.65; 95% CI, 0.51–0.84; P=.001).

A retrospective study (N=1,638) of hospitalized patients with acute stroke was performed to determine if there was an increase in venous thromboembolism (VTE), including DVT and pulmonary emboli, after the routine use of compression stockings was stopped as part of hospital practice.³ No increase in VTE was found in patients in the 2 years after the use of GCS were discontinued as compared to 2 years prior to discontinuation (3.0% vs 2.7%; P=.8). This study was limited due to being retrospective, conducted at only 1 center, and the statistics used were not defined.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the US Army at large, or the Department of Defense.


ERRATUM
In the November issue, the HelpDesk Answers article entitled, “What is the most effective management of an acute fracture of the base of the fifth metatarsal? (EBP. 2014; 17[11]:12) the city and state for authors Dae Hyoun Jeong, MD, and Janet Albers, MD, were listed incorrectly. Their correct affiliation should have been listed as Southern Illinois University School of Medicine, Springfield, Illinois. The electronic version of EBP has been updated to reflect this correctly.
Pediatric gastroesophageal reflux disease (GERD)

Pathophysiology

1. Incidence/prevalence
   - GERD: 10%–20% children
     - Peak incidence at 4 months; usually self-resolves by 12–18 months

2. Risk factors
   - Preterm
   - Obesity
   - Chronic lung disease
   - Achalasia, hiatal hernia
   - Neurological impairment

Diagnostics

1. History
   - Infants
     - Spitting up, irritability, failure to thrive, stridor/wheezing/recurrent pneumonia
   - Toddlers/preschool age
     - Vomiting/abdominal pain
     - Poor appetite/feeding refusal
   - Children/adolescents
     - Abdominal/chest pain
     - Sour burps
     - Wheezing/recurrent pneumonia/sinusitis

2. Physical exam
   - Coughing/wheezing
   - Apnea and bradycardia

3. Diagnostic testing
   - Endoscopy (SOR: C)
   - Esophageal pH meter or manometry

4. Laboratory evaluation
   - CBC, UA, electrolytes, urea/creatinine, celiac screening (SOR: C)

5. Diagnostic imaging
   - Barium or Tc99 swallow (SOR: B)

Therapeutics

1. Therapeutic lifestyle changes (TLC)
   - 59% with clinical improvement by 2 weeks
   - Avoid tobacco smoke
   - Infant
     - Position
       - Upright after feeding
       - No prone sleeping (SIDS risk) (SOR: A)

2. Medical therapy
   - TLC failure
   - Medicate early if heartburn/asthma (SOR: B)
   - Proton pump inhibitors (PPIs) first line
     - Not recommended if primary infant symptoms are cough/crying/irritability (SOR: A)
     - Adolescents: 4-week trial, then 3-month course if symptoms resolve (SOR: D)
     - No PPI proven superior
     - Omeprazole
       - 2–16 years
     - Esomeprazole/lansoprazole
       - 1–17 years
     - H2 blockers
       - Less effective than PPI (SOR: A)
     - Prokinetic medications
       - Adverse effects outweigh benefit (SOR: C)

3. Surgical treatment
   - Only if failed medical therapy or high aspiration risk (SOR: C)

REFERENCES

Is modafinil safe and effective at improving mental performance in shift workers?

Bottom line
Modafinil decreases attention lapses and minimally improves subjective mental state in shift workers (SOR: B, 2 limited RCTs). However, drug monitoring agencies have issued warnings about its safety based on associations with serious cutaneous, psychiatric, and cardiovascular events leading to more restrictive indications (SOR: C, expert opinion).

Evidence summary
A 12-week, double-blinded RCT (N=209) evaluated the effectiveness of modafinil 200 mg versus placebo given 30 to 60 minutes prior to 3 simulated night shifts in patients aged 18 to 60 years with shift work sleep disorder (SWSD). Inclusion criteria were ≥5 night shifts per month with ≥3 consecutive shifts and ≥3 months of excessive sleepiness during night shifts.

The only outcome pertaining to mental performance was lapses of attention measured by four 20-minute Psychomotor Vigilance Tests, which are not validated for SWSD. Patients were required to promptly press a button at a random cue. During the simulated shift, modafinil significantly decreased the median number of lapses of attention versus placebo (10 vs 24; P<.001). Insomnia was the only adverse event that was statistically different versus placebo (6% modafinil vs 0% placebo; P<.01). The trial was limited with only 75% of original participants completing all 3 simulated night shifts.

A second 12-week double-blinded RCT with identical inclusion criteria (N=278) evaluated the effect of modafinil on functioning in adults (age range 18–60 years) with SWSD. Modafinil 200 or 300 mg given 30 to 60 minutes before night shifts was compared with placebo. Mental state was assessed at baseline and at weeks 4 and 12 using the 36-item Short Form Health Survey (SF-36), a subjective survey scoring physical and mental health characteristics from 0 to 100, with higher scores correlating to an improved subjective mental state.

The modafinil groups showed small but significant improvements in the mental component portion of the SF-36. Mean increases from baseline in the 200-mg modafinil, 300-mg modafinil, and placebo groups were 3.7, 3.2, and 0.7 points, respectively (P<.05 for each modafinil group vs placebo; CI not reported). The trial was limited with only 65% to 74% of original participants available at conclusion.

Recommendations
In 2007, the US FDA released an updated warning on modafinil citing postmarketing reports of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme. Although these reports are rare—6 cases in the United States in 8 years—this exceeded the background incidence rate.

In 2011, the European Medicines Agency (EMA) issued a recommendation to restrict the indication for modafinil to narcolepsy, citing rare but serious cutaneous (SJS, TEN), psychiatric (suicidal thoughts, depression, psychosis), and cardiovascular events (hypertension, irregular heartbeat). The EMA referenced numerous preclinical and clinical trials, published literature, and postmarketing data, including 5,849 patients from the Marketing Authorization Holder’s pharmacology vigilance database and concluded that the risk-to-benefit balance was, “not positive under normal conditions of use for excessive sleepiness associated with shift work sleep disorder.”

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REFERENCES
1. Which of the following statements is true regarding the Mediterranean style diet (MSD)?
   - a. Increased adherence to the MSD has been shown to reduce a person’s risk of cardiovascular disease and overall mortality
   - b. The MSD has not been shown to be effective in improving overall mortality in patients with a history of previous myocardial infarction
   - c. Studies of the MSD have been too small to demonstrate benefit that reaches the level of statistical significance
   - d. The MSD has not been studied in populations with multiple cardiovascular risk factors

2. What is the most common cause of gastroparesis in both adults and children?
   - a. Medications
   - b. Diabetes
   - c. Idiopathic
   - d. Postsurgery

3. All of the following statements are true regarding modafinil use in shift work sleep disorder except:
   - a. Modafinil has been shown to decrease lapses in attention
   - b. Modafinil improves mental state scores on the 36-item Short Form Health Survey
   - c. Modafinil has been shown to be an effective treatment for insomnia
   - d. Modafinil has been associated with postmarketing cases of toxic epidermal necrolysis

4. Which is true regarding the workup of angioedema and urticaria?
   - a. If no etiology is evident, CBC, CMP, UA, stool studies, and complement levels are reasonable initial tests
   - b. Evidence is insufficient to recommend any particular workup, but it may be guided by a thorough history and physical
   - c. Everyone who has angioedema and urticaria should undergo skin-prick testing to determine the causative agent(s)
   - d. There is never a need to check for a C1 esterase inhibitor deficiency, as that is treated like idiopathic urticaria

5. Which of the following statements is true about deep vein thrombosis (DVT) prophylaxis in hospital patients with acute stroke?
   - a. Intermittent pneumatic compression devices have been shown to decrease DVT risk
   - b. Thigh-length graduated compression stockings have been shown to decrease DVT risk
   - c. Intermittent pneumatic compression devices have been shown to increase DVT risk
   - d. Thigh-length graduated compression stockings have been shown to increase DVT risk

6. The parents of your 10-year-old patient call to ask you about weighted vests for attention deficit hyperactivity disorder (ADHD). You inform them that, based on current evidence:
   - a. Weighted vests do not show any benefit for the treatment of ADHD symptoms
   - b. A weighted vest may help their child stay on-task in school
   - c. Behavioral therapies are clearly a better option than wasting money on a weighted vest
   - d. A weighted vest will help their child be less vocally disruptive in school

7. Which of the following statements is true regarding leukotriene receptor antagonists for the treatment of acute asthma exacerbation?
   - a. They are associated with a decrease in hospitalizations
   - b. They are associated with a decrease in FEV1
   - c. They may decrease the duration of therapy
   - d. They decrease the time to eliminate all asthma symptoms

8. Which of the following statements is true about the use of nicotine replacement therapy for pregnant patients?
   - a. It is the first-line intervention for smoking cessation
   - b. It is more effective for reducing adverse fetal outcomes than other treatments
   - c. It is as effective as cognitive behavioral therapy and stage of change
   - d. It is considered FDA pregnancy category A

For each question, please mark the single best answer by checking the appropriate box. To receive CME credit, a minimum score of 75% (6 out of 8 correct) is required.

Answer key: 1. a; 2. c; 3. c; 4. b; 5. a; 6. b; 7. c; 8. c
What do YOU see in the future of Evidence-Based Practice?

- [ ] Increased relevancy?
- [x] Medline indexing?
- [ ] An App?
- [ ] All of the above?

Please take our short online survey and tell us! Go to http://fluidsurveys.com/s/2014EBP/ and let us know your thoughts.
How should a positive urine urobilinogen dipstick test be evaluated?

Evidence-Based Answer

A positive urine urobilinogen test (≥3 mg/dL) does not have adequate sensitivity or specificity to function as a reasonable screening test for liver or biliary tract disease (SOR: C, based on 3 prospective, observational cohort studies).

A series of 3 prospective observational studies were published in the late 1980s to examine the usefulness of urine urobilinogen assays to screen for the presence or absence of liver or biliary tract disease. All 3 studies were conducted at a city-county hospital in El Paso, Texas. Patients of any age, sex, or ethnicity presenting to the emergency department for any reason had both serum liver function tests (LFTs) and urine Chemstrip 9 assay of urine sent for analysis.

In the first trial (N=122), using cutoff values of ≥4 mg/dL as abnormal and ≤2 mg/dL as normal, sensitivity for positive urobilinogen and any LFT abnormality was only 51%, while specificity for any LFT abnormality was 87% (positive likelihood ratio [LR+] 3.9 and negative likelihood ratio [LR–] 0.57). Likewise, urine urobilinogen results were not a strong indicator of elevated serum alkaline phosphatase (sensitivity 53%; specificity 77%; LR+ 2.2; LR– 0.62).1

In 2 subsequent prospective cohort studies published in 1988 (N=324) and 1989 (N=229), the abnormal cutoff value was set slightly differently at ≥3 mg/dL; however, study outcomes were similar (TABLE).2,3

In all 3 trials, urine urobilinogen testing was found to be more sensitive in detecting serum bilirubin elevations (sensitivity of 72%–78%, specificity 80%–84%); however, likelihood ratios remained low (LR+ 3.6–4.9; LR– 0.26–0.36).1–3 Potential limitations for these studies included low generalizability (given the populations of study were predominately Hispanic with a disproportionate incidence of biliary tract disease, intravenous drug abuse, and viral hepatitis) and the use of a specific assay for testing urine (Chemstrip 9 assay).

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### TABLE

**Accuracy of urinary urobilinogen in diagnosing elevated LFTs**

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<tr>
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<td>Sensitivity for any LFT abnormality</td>
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<td>Specificity for any LFT abnormality</td>
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<td>LR+</td>
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LFT=liver function test; LR+=positive likelihood ratio; LR–=negative likelihood ratio
Does reduction or modification of dietary fat intake decrease rates of myocardial infarction, stroke, or death in patients?

Evidence-Based Answer

In mixed-risk populations, reduction or modification of dietary fat does not decrease the incidence of myocardial infarction (MI) or stroke, nor does it decrease cardiovascular or total mortality (SOR: A, meta-analysis). Reducing saturated fat, however, may decrease the risk of stroke in high-risk individuals (SOR: B, RCT). A reduced saturated fat diet in individuals with cardiovascular risk factors may decrease the risk for overall cardiovascular events (SOR: B, RCT and subanalysis within a meta-analysis).

A 2012 Cochrane meta-analysis of 48 RCTs of adult men and women older than 18 years with varying levels of cardiovascular risk examined the effects of reducing or replacing dietary saturated fat with unsaturated fats compared with a usual or control diet for at least 6 months on total mortality, cardiovascular mortality, and combined cardiovascular events. Combined cardiovascular events were specified to include any of the following: cardiovascular deaths, nonfatal MI, stroke, angina, heart failure, peripheral vascular disease, atrial fibrillation, angioplasty, and coronary artery bypass grafting.

In the analysis of individual outcomes, altering dietary fat intake had no clear effect on the incidence of MI (19 trials, N=64,891; RR 0.93; 95% CI, 0.84–1.0), the incidence of stroke (11 trials, N=59,853; RR 0.99; 95% CI, 0.89–1.1), total mortality (21 trials, N=71,790; RR 0.98; 95% CI, 0.93–1.0), or cardiovascular mortality (16 trials, N=65,978; RR 0.94; 95% CI, 0.85–1.0). However, there was a 14% reduction of combined overall cardiovascular events (23 trials, N=65,508; RR 0.86; 95% CI, 0.77–0.96), suggesting a protective effect of dietary fat manipulation.

A 2013 parallel-group, multicenter, randomized, single-blinded trial in Spain compared a Mediterranean diet supplemented with olive oil or nuts with a control diet over 4.8 years. The trial included 7,447 patients aged 55 to 80 years with no current cardiovascular disease but classified as high risk, either having type 2 diabetes mellitus or at least 3 of the following risk factors: smoking, hypertension, elevated low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obese, or a family history of premature coronary heart disease. One limitation of the study was that the groups were statistically different at the start of the study.

The primary endpoint was defined as the composite rate of MI, stroke, and death from cardiovascular cause. Secondary endpoints were rates of stroke, MI, death from cardiovascular causes, and death from any cause.

The primary endpoint of combined overall cardiovascular events was lower with the Mediterranean diet than the control diet (HR 0.70; 95% CI, 0.55–0.89). Of the secondary measures, only individual stroke reduction (HR 0.61; 95% CI, 0.44–0.86) in the Mediterranean diet arm versus the control group was found to be significant. No significant difference was found for MI (HR 0.77; 95% CI, 0.52–1.2), cardiovascular death (HR 0.83; 95% CI, 0.54–1.3), or all-cause mortality (HR 0.89; 95% CI, 0.71–1.1).

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the US Army at large, or the Department of Defense.


GLOSSARY

ARR=absolute risk reduction
CDC=Centers for Disease Control and Prevention
CI=confidence interval
CT=computed tomography
FDA=US Food and Drug Administration
HR=hazard ratio
LOE=level of evidence
MRI=magnetic resonance imaging
NNH=number needed to harm
NNT=number needed to treat
NSAID=nonsteroidal anti-inflammatory drug
OR=odds ratio
RCT=randomized controlled trial
RR=relative risk
SOR=strength of recommendation
SSRI=selective serotonin reuptake inhibitor