ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 8 | August 2017

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the
Family Physicians Inquiries Network

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Family Physicians Inquiries Network

FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.

Diminished discrimination

I have reached that special age when small type is becoming more difficult to read. I have tried a number of compensation measures—seeking brighter light, holding printed material a little further away, and even furtively donning those $10 reading glasses from the drug store. But the handwriting is on the wall—and I can no longer read it.

That doesn't mean I want to admit it. I am okay pulling out my readers when I'm in the exam room with a 90-year-old patient—it confirms we are walking the long road of life together. But I'd rather not pull them out when working with the younger faculty, because they might sense some vulnerability. I don't worry about using my readers when I'm around the residents, though. The residents think I'm old no matter what I do.

With time, diminished discrimination has inevitably come to my eyesight. With time, perhaps just as inevitably, decreased discrimination also occurs in clinical risk prediction tools. "How's that?" you ask. Well...

A team of researchers decided to see what kind of external validation was applied to 127 new clinical prediction models.[1] As you know, a prediction model needs to be validated by a different team from the one that developed it. The researchers found that an external validation study had been done for a paltry 25% of the new models. Worse still, completely independent validation (with no author overlap) occurred only 17% of the time.

A curious, but not entirely unexpected thing also happened when a new team tried to validate the tool—on average, the discrimination of the tool decreased; it never got better. Specifically, the median area under the ROC curve dropped by 0.04 (P<.01) with later independent validation.[1]

If this effect sounds sort of familiar, it should. The magnitude of effect often decreases between the first RCT and the meta-analysis, between the pilot and the subsequent big study, and between early trials and the later ones.

Once again, we clearly see the curious actions of probability and bias on a body of research. At least, I hope you clearly see it. I need to find my readers.

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STATEMENT OF PURPOSE

Evidence-Based Practice (EBP) addresses important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format. Our goal is to instruct our authors on how to write peer-reviewed scholarly research for the medical and scientific community.

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DISCLOSURE

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

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Is it safe for patients to remain on antiplatelet medication for a screening colonoscopy?

EVIDENCE-BASED ANSWER

The answer depends on the specific antiplatelet medication. Aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) do not increase postpolypectomy bleeding (PPB) after colonoscopies, while clopidogrel (either alone or with ASA or NSAIDs) significantly increases the absolute risk of PPB (SOR: **B**, meta-analysis of case-control studies). ASA or NSAIDs can be continued for any colonoscopy, but clopidogrel should be withheld to allow for safe polypectomy (SOR: **C**, expert opinion).

Evidence summary

A 2015 systematic review with meta-analysis of 6 retrospective case-control studies evaluated PPB in 12,427 patients taking antiplatelet medications.[1] PPB was defined as the presence of overt bleeding with melena, hematochezia, and/or a decrease in hemoglobin of at least 2 g/dL. PPB was either immediate (occurring during the procedure) or delayed (occurring ≤30 days of the procedure).

ASA or NSAIDs

Four retrospective case-control studies evaluated PPB in 1,489 patients taking ASA and/or NSAIDs and 3,650 matched controls not taking ASA and/or NSAIDs (specific medications and doses not reported). PPB occurred in 3.9% of the patients in the ASA/NSAID group compared with 2.8% in the control group (no statistical difference between groups). No statistical difference was noted in a subgroup analysis of immediate or delayed PPB (see **TABLE**).[1]

Clopidogrel

Two retrospective case-control studies compared the incidence of PPB in 95 patients taking clopidogrel (doses not reported) and 2,780 controls not taking clopidogrel. PPB occurred in 7.4% of the patients in the clopidogrel group compared with 0.97% in the control group. In subgroup analysis, a significant difference was present in both immediate PPB and delayed PPB (see **TABLE**) when compared with the control groups.[1]

Dual antiplatelet therapy (DAT)

Two retrospective case-control studies compared the incidence of PPB in 260 patients taking DAT, which included clopidogrel and ASA/NSAIDs and 3,092 controls not on DAT. ASA was the dual agent in 78% of patients in 1 of these studies and in 54% of patients in the other. The latter study evaluated immediate PPB and found no significant difference between cohorts (see **TABLE**). Delayed bleeding was increased in the DAT group in pooled data from both studies (see **TABLE**).[1]

TABLE

Rate of postpolypectomy bleeding (PPB) in patients using antiplatelet medications[1]

Antiplatelet medication	Immediate PPB			Delayed PPB		
	No. of case-control studies (no. of patients)	Control	Active medication	No. of case-control studies (no. of patients)	Control	Active medication
ASA/NSAIDs	2 (N=4,281)	1.3%	1.6%	4 (N=5,139)	2.5%	3.6%
Clopidogrel alone	1 (N=2,450)	0.3%	4%[a]	2 (N=2,875)	0.6%	4%[a]
DAT	1 (N=1,385)	1%	2%	2 (N=3,352)	0.6%	2%[a]

[a]Statistically significant difference compared with control (*P*<.01).

ASA=aspirin; DAT=dual antiplatelet therapy with clopidogrel plus ASA or NSAIDs; NSAIDs=nonsteroidal anti-inflammatory drugs; PPB=postpolypectomy bleeding.

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Diabetes self-management education: Looking for better choices

Lorig K, Ritter PL, Turner RM, English K, Laurent DD, Greenberg J. Benefits of diabetes self-management for health plan members: a 6-month translation study. *J Med Internet Res*. 2016; 18(6):e164.

This nonblinded uncontrolled study measured the effectiveness of a curriculum teaching diabetes self-management based on the Better Choices, Better Health-Diabetes guidelines. Patients were recruited to an Internet or face-to-face community-based program. Questionnaires and mail-in labs were used to collect data on 14 variables (eg, hemoglobin A1C; depression; hypoglycemic symptoms; sleep; and routine eye, foot, and kidney examinations) over 6 months.

The population was a heterogeneous sample; all participants had insurance and a high education level. Patients were required to have type 2 diabetes and be on an Anthem Medicare program. No inclusion criteria specified disease duration or severity.

The primary outcome was an adjusted effect size of change >0.4 (the mean change divided by the standard deviation) in any 1 variable at 6 months.

Although 10 of the variables had a statistically significant 6 month mean change, no single variable reached the goal effect size change of >0.4. Individually, 75% (662 of 1,242) of patients achieved the adjusted effect size of change in at least 1 of the observed variables. In summary, no clinically relevant improvements in patient-oriented outcomes were demonstrated through this specific implementation of the Better Choices, Better Health-Diabetes program.

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

Bottom line: The study did not show any clinically significant improvements in diabetes outcomes with the Better Choices, Better Health-Diabetes program in a heterogeneous population that may not be generalizable.

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Want to lose weight? Don't count those steps

Jakicic JM, Davis KK, Rogers RJ, King WC, Marcus MD, Helsel D, et al. Effect of wearable technology combined with a lifestyle intervention on long-term weight loss: the IDEA randomized clinical trial. *JAMA*. 2016; 316(11):1161–1171. Erratum in: *JAMA*. 2016; 316(14):1498.

A 2016 RCT with 470 overweight adults (body mass index 28–35 kg/m^2) aged 18–35 years examined the effectiveness of wearable technology devices that monitor physical activity for long-term weight loss.

All patients received a behavioral weight loss intervention for 6 months, and then telephone counseling sessions, text message prompts, and website materials were added. After 6 months, patients were randomized to either a standard group, which included all of the above and self-monitoring of diet and exercise, or an enhanced group, which received wearable technology connected to a web-based interface to monitor physical activity and diet. All patients were prescribed 100 minutes of physical activity per week and increased at 4-week intervals to a goal of 300 minutes per week. The median day count the device was worn was 170 days and the mean time was 241 minutes per day.

At 24 months, the standard group lost more weight than the enhanced group (–5.9 vs –3.5 kg; mean difference [MD] –2.4; 95% CI, –3.7 to –1.0) and had a larger percent weight change from baseline (–6.4% vs –3.6%; MD –2.8%; 95% CI, –4.2 to –1.5). Approximately 79% of participants in each group completed the 24 months.

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

Bottom line: The use of wearable technology to monitor physical activity did not lead to increased weight loss in this population of patients. Recommending this type of technology is not the standard, and this study showed that the device may not help patients lose weight. In addition, not all patients will have access to these types of electronic resources. EBP

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How does exclusive breastfeeding affect risk of postpartum depression?

Bottom line

Risk of postpartum depression (PPD) is decreased with exclusive breastfeeding, particularly in patients who express an interest in doing so before delivery. Patients with prenatal depression also have lower rates of PPD if they breastfeed.

CASE

Kris, a 25-year-old woman at 36 weeks' gestation, bottle-fed her first infant and had PPD for 1 year. She is considering breastfeeding this time, but is concerned about her risk of repeat PPD. She asks for recommendations.

Evidence summary

PPD affects 13% to 19% of women who have recently given birth.[1] The World Health Organization, American Academy of Pediatrics, and the European Commission Directorate for Public Health have all recommended exclusive breastfeeding for ≥6 months as the optimal infant feeding method.[1] A possible association between breastfeeding and PPD has been assessed in several studies, but no RCTs or systematic reviews have clarified the direction of this relationship.

A 2015 longitudinal cohort study evaluated about 14,000 children in England.[2] Data from the Edinburgh Postpartum Depression Scale (EPDS) were collected during and after pregnancy, along with prenatal intent and postnatal actual method of infant feeding.

Overall, longer durations of breastfeeding and exclusive breastfeeding were associated with a lower risk of PPD, although the difference was not significant. For mothers who were not depressed during pregnancy, the lowest risk of PPD was found among women who had planned to breastfeed and who had actually breastfed their babies (odds ratio [OR] 0.36; 95% CI, 0.18–0.71).[2]

The highest risk of PPD was among women who had planned to breastfeed and had not gone on to breastfeed (OR 2.55; 95% CI, 1.34–4.84). PPD risk was also higher among women who had not planned to breastfeed, but did go on to breastfeed—but this risk was significant only at 21 months. In mothers who had shown signs of depression before or during pregnancy, the protective effects of breastfeeding as planned were smaller but still present; however, the only significant effect on the week 8 EPDS was for at least 4 weeks' exclusive breastfeeding (OR 0.42; 95 % CI, 0.20–0.90).[2]

In a 2014 prospective cohort study, 145 women completed the EPDS during pregnancy, neonatal period, and 3 months postpartum.[3] Self-report exclusive breastfeeding data were collected at birth and at 3, 6, and 12 months postpartum.

A decrease in depression scores was seen from birth to 3 months postpartum in women who exclusively breastfed for ≥3 months, but results were not statistically significant. No change was seen in women who did not initiate breastfeeding or who stopped exclusive breastfeeding early.[3]

A 2009 systematic review identified 49 research articles evaluating breastfeeding and PPD.[4] Seven studies found that breastfeeding was associated with lower levels of depression and 7 studies found an association between bottle feeding and higher levels of PPD. Twelve studies suggested that maternal mood may have a greater influence on breastfeeding outcomes than breastfeeding on mood. Study limitations were related to the multiple study designs.

A 2015 systematic review identified 48 relevant studies including 71,245 mothers.[5] Six studies found that breastfeeding initiation and longer duration decreased PPD symptoms versus bottle feeding. Five studies indicated that depression preceded breastfeeding cessation. The research was equivocal regarding the predictive value of breastfeeding on PPD.

CASE WRAP-UP

Because Kris had already expressed an interest in breastfeeding, you support her choice during prenatal visits. Kris breastfeeds exclusively for 6 months and has no recurrence of PPD. EBP

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How predictive are fetal kick counts for assessing fetal well-being?

EVIDENCE-BASED ANSWER

The utility of fetal kick counts in predicting fetal well-being remains unclear. Fetal kick counting does not alter rates of Cesarean section, neonatal intensive care unit (NICU) admissions, or low Apgar scores compared with standard care; however, they may increase antenatal hospital admissions and identification of growth-restricted fetuses. Once-daily counting results in better compliance than other methods, without increasing the rate of Cesarean section (SOR: **B**, based on a systematic review and 1 prospective cohort study).

A 2015 systematic review evaluated 5 RCTs (N=71,458 pregnant women) studying the effectiveness of fetal kick count assessment for predicting fetal well-being.[1] Primary outcomes assessed in the review included Cesarean section, neonatal death, NICU admission, and encephalopathy. Three trials compared formal fetal movement assessment instruction with "standard care" (not defined) or hormone assessment of fetal well-being in women with singleton pregnancies recruited between 28 and 32 weeks' gestation, and 2 trials compared 2 different methods of fetal movement counting (1 trial included women in a high-risk OB practice).

No difference was found in nonelective Cesarean sections comparing modified count-to-10 fetal movement assessment versus "standard care" (1 trial, n=1,076; risk ratio [RR] 0.93; 95% CI, 0.60–1.4). No difference in Cesarean rate was found when comparing formal fetal movement counting with hormone analysis to assess fetal well-being (1 trial, n=1,191; RR 1.2; 95% CI, 0.83–1.7). Another trial that compared once-daily fetal movement counting using the count-to-10 method with multiple episodes of counting per day found no difference in Cesarean section rates between both groups (1 trial, n=1,400; RR 0.92; 95% CI, 0.56–1.5), but did note increased compliance among women who were instructed to count only once per day. No perinatal deaths were reported in this study.[1]

None of the studies in the review compared outcomes after fetal movement counting with outcomes in women who were specifically instructed not to count movements. No study reported on the primary composite outcome of neonatal morbidity and mortality. The rate of antenatal hospital admissions because of perceived decreased fetal movement was higher in women who were instructed in formal fetal movement assessment than in standard care (1 trial; n=1,076; RR 2.7; CI, 1.3–5.5). Growth-restricted fetuses were more often identified prior to birth in the fetal movement group than in the control group (1 trial; n=1,076; 87% vs 60%, respectively; *P*=.046). The overall proportion of small-for-gestational-age (SGA) fetuses (defined as <10th percentile birthweight) was similar between interventions and controls (1 trial; n=1,076; RR 0.98; 95% CI, 0.66–1.4). This trial did not find any difference between the 2 groups for secondary outcomes of premature birth, 5-minute Apgar score <4, or NICU admission. No perinatal deaths were reported.[1]

A prospective cohort study of 1,786 women with low-risk singleton pregnancies (defined as nonsmoking mother with prepregnancy body mass index <28 kg/m^2) compared fetal movement counting in pregnancies with normal outcomes versus those with suboptimal outcomes, defined as SGA infant (<10th percentile for birthweight), transfer to NICU, preterm birth (28w 0d to 36w 6d), or nonelective Cesarean section.[2] All women received formal instruction in fetal movement counting using a standardized fetal movement chart. A modified count-to-10 protocol was used, wherein women were instructed to begin counting when the first movement was perceived, and then to record the number of minutes required to perceive an additional 9 movements. Median compliance rate overall was 97%.

The percentage of women who ever reported decreased fetal movement (defined as <10 movements within 2 hours) did not differ between both groups (5% for pregnancies with suboptimal outcomes vs 4% for pregnancies with normal outcomes). Generalizability may have been limited due to homogeneity and low-risk pregnancy status of the sampled population.[2]

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In East Asian American adults, does routine screening with EGD reduce morbidity and mortality from gastric cancer?

EVIDENCE-BASED ANSWER

East Asian patients screened with esophagogastroduodenoscopy (EGD) are more likely to have low-grade lesions and lower rates of death from gastric cancer within the first 5 years of diagnosis (8% vs 43% in unscreened patients) (SOR: **B**, cohort studies at risk of lead-time bias). Screening EGD should be considered in first-generation immigrants from high-risk regions with family history of gastric cancer in a first-degree relative (SOR: **C**, expert opinion).

In 2014, a retrospective cohort study of (N=846) evaluated the association of screening intervals with the stage of identified gastric neoplasms.[1] Patients were all living in Korea and older than 39 years (mean age 61 years). Men comprised about two-thirds of patients. Neoplasms were identified as advanced gastric cancer or early gastric cancer, defined as one treatable with endoscopic submucosal dissection.

As the interval between EGD screenings decreased, the proportion of neoplasms treated with submucosal dissection increased. In the EGD interval groups of none within 5 years, 36–60 months, 24–36 months, 12–24 months, and ≤12 months, the number of lesions treated with endoscopic submucosal dissection were 27%, 38%, 50%, 52%, and 55%, respectively. The largest effect of shortening interval was seen between the 24- to 36-month group (50%) and the 36- to 60-month group (38%).[1]

Limitations of the study included the retrospective format and recall bias, as screening interval was determined by questionnaire survey of patients diagnosed with gastric neoplasms. Another limitation was the disease-oriented nature of the data presented and possible lead-time bias.[1]

In 2008, a retrospective cohort study in Japan evaluated mortality in 11,763 patients with and without EGD screening.[2] Patients were recruited from the Fukui Prefectural Hospital medical center from 1990 to 1992. Patients screened with other methods as well as patients with gastric disorders were excluded from the study.

Of the 11,763 patients, 2,192 were examined using screening EGD in the outpatient setting and 9,571 were not. The patients were Japanese adults 40 to 74 years old. The screened group consisted of 64% men and had a mean age of 52 years. The nonscreened group was 47% men and had a mean age of 56 years.[2]

Over 10 years in the screened group, 63 patients (2.9%) were diagnosed with gastric cancer versus 147 (1.5%) in the unscreened group. Within 5 years of diagnosis, 5 patients died from gastric cancer in the screened group versus 63 in the unscreened group, for death rates of 8% and 43% (risk ratio [RR] 0.35; 95% CI, 0.14–0.86). In male patients, there were 3 deaths from gastric cancer in the screened group versus 44 deaths in the unscreened group (RR 0.22; 95% CI, 0.0–0.70). This study was also subject to possible lead-time bias.[2]

In 2010, the American Society for Gastrointestinal Endoscopy published consensus guidelines on ethnic issues in endoscopy.[3] They recommend that for first-generation immigrants from high-prevalence countries with affected first-degree relatives, screening EGD "should be considered."

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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 Air Force Medical Department, the Air Force at large, or the Department of Defense.

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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 ground-breaking research is changing the practice of family medicine.

3 To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.

In patients with known coronary artery disease or cardiovascular risk factors, does daily consumption of berries decrease the risk of heart attack?

EVIDENCE-BASED ANSWER

In patients with risk factors for coronary artery disease, daily berry consumption results in small decreases in systolic blood pressure and small increases in high-density lipoprotein (HDL) cholesterol levels. In patients with diabetes, cranberry extract powder leads to small decreases in total and low-density lipoprotein (LDL) cholesterol levels. The effect of berries on patient-oriented outcomes such as heart attacks is unknown (SOR: **C**, small RCTs with disease-oriented outcomes).

In 2008, a single-blind RCT evaluated 72 middle-aged Finnish adults to determine the effects of daily berry use versus placebo on blood pressure and lipid profiles.[1] Patients had at least 1 of the following conditions: hypertension, hyperglycemia, or dyslipidemia (elevated total cholesterol, elevated triglycerides, or low HDL). Patients were excluded if they were currently taking medications for the above conditions, took other supplements, smoked, or were obese.

The berry group consumed various types of berries as whole berries, purees, nectars, and juice preparations. The placebo group consumed 2 dL sugar-water, 100 g sweet semolina porridge, 100 g sweet rice porridge, or 40 g marmalade sweets. Patients consumed 2 servings of placebo or berries daily. All participants were instructed to maintain their normal diets and to avoid consuming berries from other sources not provided in the study. Patients had blood work and blood pressures collected at the start of the study and after 8 weeks.[1]

Berry consumption was associated with a small but statistically significant decrease in systolic blood pressure by 1.5 mmHg versus a 0.5-mmHg increase in the placebo group (P=.050). The berry group had a 5.2% increase in HDL versus a 0.6% increase in the placebo group (P=.006). No adverse events were described in this study.[1]

A 2008 double-blind RCT evaluated 30 Taiwanese adults aged 50 to 75 years with type 2 diabetes to determine the effect of cranberry supplementation versus placebo on lipid profiles.[2] Patients taking insulin were excluded. Patients could continue to use other medications for diabetes, hypertension, and dyslipidemia, provided there were no changes to the medications in the 4 weeks prior to starting or during the time of the trial. Baseline lipid profiles showed total cholesterol of 205 mg/dL in the cranberry group and 197 mg/dL in the placebo group; HDL cholesterol of 50 mg/dL in both groups; and a total cholesterol to HDL ratio of 4.3 in the cranberry group and 4.0 in the placebo group. Patients took 500 mg cranberry extract powder capsules or placebo 3 times a day after each meal.

After 12 weeks, cranberry extract use resulted in a small decrease in LDL (–7.2 vs 3.6 mg/dL; P<.001), total cholesterol (–7.2 vs 5.4 mg/dL; P<.001), and the total cholesterol to HDL ratio (–5.4 vs 1.8 mg/dL; P=.032) compared with placebo. No adverse events were described in the study.[2]

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Is physical therapy better than surgery for carpal tunnel syndrome?

EVIDENCE-BASED ANSWER

No, the treatments are likely to have equivalent outcomes. Physical therapy (PT) yields less pain at 1 and 3 months than surgery, but this difference disappears by 6 months. Surgery leads to improvement in some measures of function and symptom severity at 12 months, but the differences are likely not clinically significant (SOR: **B**, 2 RCTs with inconsistent conclusions).

A 2015 RCT evaluated surgery versus PT for relief of pain in 120 women diagnosed with carpal tunnel syndrome (CTS) at a hospital in Madrid, Spain.[1] Patients had at least 12 months of night pain and paresthesia, positive Tinel and Phalen signs, or electromyography (EMG) showing sensory and motor deficits in the median nerve.

Sixty patients allocated to PT received three 30-minute sessions per week of manual therapy consisting of soft-tissue mobilization, nerve gliding, and tendon gliding. Three patients eventually crossed over to surgery. Sixty patients underwent open or endoscopic surgery. The primary outcome measure was an 11-point Numerical Pain Rating Scale, with a score of 0 indicating no pain and a score of 10 indicating maximum pain. A change of 2 points was defined as the minimal clinically important difference. Patients reported current hand pain and worst pain in the last week.[1]

At 1 month, the PT group improved from baseline 2.0 points more than the surgery group in mean current pain (95% CI, 1.2–2.8) and 2.9 points more in worst pain (95% CI, 2.0–4.0). At 3 months, the PT group showed more improvement from baseline than surgery for both current pain and worst pain (current pain 1.3 points, 95% CI, 0.6–2.1; worst pain 2.0 points, 95% CI, 0.9–3.0). At 6 and 12 months, no significant difference was noted in pain between PT and surgery.[1]

In 2009, another RCT evaluated surgery versus PT for treatment of CTS. Patients (N=116) were referred for possible surgical repair at 7 facilities in the United States, with more than 50% from 1 facility.[2] Patients had numbness or tingling in at least 2 digits on 1 hand lasting longer than 2 weeks or EMG showing increased motor latency or sensory difference.

Fifty-seven patients were assigned to open or endoscopic surgery (77% completed surgery). Fifty-nine patients were assigned to PT with 6 hand therapy sessions over 6 weeks consisting of ligament stretching, tendon gliding, night splinting, and activity modification as well as concurrent NSAID therapy. Patients without improvement at 6 weeks were offered 12 sessions of focused ultrasound (1 MHz pulsed, 12 minutes/session). Eventually, 33% of patients in the PT group crossed over to surgery. The primary outcome measure was the Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) with 1-to-5 scales for both function and symptom severity, with 1 indicating no functional limitations or symptoms, and 5 indicating extreme limitation or symptom severity.[2] A clinically important difference is variably reported to be at least 0.47 or 0.74.

At 6 months and 12 months, surgery showed a 0.46 (95% CI, 0.20–0.72) and 0.40 (95% CI, 0.11–0.70) greater decrease in the functional limitation component of the CTSAQ compared with PT. Although no difference in the symptom severity component of the CTSAQ was noted at 6 months, surgery showed a 0.34 (95% CI, 0.02–0.65) greater decrease compared with PT at 12 months. At 12 months, surgery and PT did not differ in pain intensity, days of lost work, days of reduced work/housework, or pain interference with work/housework.[2]

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Does the treatment of obstructive sleep apnea with continuous positive airway pressure improve heart failure outcomes?

EVIDENCE-BASED ANSWER

Maybe not. In patients with congestive heart failure (CHF), continuous positive airway pressure (CPAP) treatment of obstructive sleep apnea (OSA) has no effect on exercise capacity or New York Heart Association (NYHA) classification (SOR: **B**, small RCTs). Whether there is an effect on ejection fraction is unclear and no evidence is available concerning mortality.

A 2007 double-blind, randomized, placebo-controlled crossover trial of 26 patients with OSA and CHF examined the effect of treatment of OSA with CPAP versus sham CPAP for 6 weeks on heart failure severity.[1] Examined outcomes included sleep duration and the Epworth Sleepiness Scale (ESS, an 8-question assessment scored 0–24). Mean nightly CPAP and sham CPAP use were similar: 3.5±2.5 and 3.3±2.[2] hours, respectively (*P*=.31).

Compared with sham CPAP, CPAP had a greater reduction in the ESS score (–1; 95% CI, –1.9 to 0.0). Sleep duration for both groups was similar, at 4.6±1.5 hours. No differences were noted between the treatment and sham CPAP groups in clinical and quality-of-life (QOL) assessments, left ventricular ejection fraction (LVEF), cardiopulmonary exercise testing, 6-minute walk exercise capacity, and neurohormonal markers.

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The short duration of the study and poor CPAP compliance limited the ability to show effects on cardiovascular endpoints and sleep duration.[1]

A 2004 RCT (N=40) of 3 months' duration examined the effect of OSA treatment with nocturnal nasal CPAP compared with untreated controls on systolic heart function, blood pressure, and QOL in patients with CHF.[2]

CPAP therapy improved LVEF from baseline values in the CPAP group significantly more than the control group (5.0%±1.0% vs 1.5%±1.4%; *P*=.04). CPAP versus control also revealed QOL improvements according to responses to the Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36), in which scores range from 0 to 100 (lower scores=more disability and higher scores=less disability). SF-36 scores indicated significant improvements for the CPAP treatment group versus untreated control group in the domains of social functioning (80 vs 60; *P*=.03), vitality (62 vs 45; *P*=.02), physical role (62 vs 35; *P*=.03), and mental health (80 vs 70; *P*=.01) (SF-36 scores were estimated from a figure in the article). No significant changes were noted in systemic blood pressure or NYHA classification. Study limitations included a lack of placebo, likely QOL improvement simply from treating OSA, and a high dropout rate of 27%.[2]

A 2008 multicenter RCT of adult heart failure patients with OSA (N=45) analyzed the effect of CPAP compared with sham CPAP on LEVF, 6-minute walk test, and QOL measures.[3] At 3 months, LVEF improved with CPAP therapy versus its baseline (30%±0.8% vs 28.0%±1.5%, respectively; *P*=.01) but did not improve with sham CPAP versus its baseline (28.1%±1.7% vs 28.1%±1.5%, respectively; *P*=1.0). No significant differences were found in QOL measures or 6-minute walk test.

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In men with varicocele, does surgery improve fertility?

EVIDENCE-BASED ANSWER

Surgical correction of varicocele in infertile men with either normal or abnormal semen analysis slightly improves pregnancy rates with number needed to treat (NNT) of 17. However, the effects are inconsistent when including only men with abnormal semen analysis (SOR: **B**, meta-analyses of low-quality RCTs with inconsistent findings). Pregnancy rates as high as 45% at 1 year have been reported after microsurgical varicocelectomy (SOR: **C**, case series).

In a 2012 meta-analysis, 10 RCTs including 894 men with varicocele and unexplained infertility examined the effects of surgical repair and embolization versus delayed treatment, no surgery, or placebo on pregnancy over a 12-month period.[1] Unexplained infertility included men with normal or abnormal semen analysis. Varicoceles were confirmed by Doppler ultrasound, phlebography, or radioactive scanning.

The odds of pregnancy increased during the 12 months after varicocele treatment compared with expectant management (odds ratio [OR] 1.5; 95% CI, 1.3–2.1; number needed to treat [NNT]=17). In the subgroup of men with abnormal semen analyses, varicocele repair was even more effective (5 trials, n=505; OR 2.4; 95% CI, 1.6–3.7; NNT=7). However, heterogeneity was significant and 6 of the 10 studies did not report randomization procedures.[1]

A 2011 meta-analysis included only RCTs of men with varicocele and abnormal semen analysis and evaluated surgical correction of varicocele compared with no surgery.[2] Four RCTs (N=380) were included, all of which were in the meta-analysis above; however, the meta-analysis above included an additional study of men with abnormal semen analysis published after the search dates of this review. Abnormal semen analysis here was defined as oligozoospermia.

Although semen parameters clearly improved 1 year after surgery, surgical correction of varicocele did not improve actual pregnancy rates (4 trials, n=380; OR 2.2; 95% CI, 0.86–5.8).[2]

A 2015 retrospective case series (N=145) conducted in China evaluated the effect of microsurgical varicocelectomy

on semen quality and pregnancy rates.[3] Men with abnormal semen analysis, defined by sperm concentration <20 million/mL or <50% progressively motile sperm, and varicocele on ultrasound were followed for an average of 21 months after surgery.

Of the 145 female partners, 66 (45%) had become pregnant by a year. Preoperative sperm concentrations >20 million/mL were associated with a pregnancy rate of 57%; for partners of patients with lower initial sperm concentrations (<20 million/mL), the pregnancy rate was 32%. The study was limited by being a single-center study with no control group for comparison.[3]

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Is hip or knee arthroplasty effective in promoting weight loss?

EVIDENCE-BASED ANSWER

Total knee and total hip arthroplasty do not appear to result in consistent weight loss in the postoperative period; only 14% to 49% of patients lost weight and most patients stayed the same weight or gained weight (SOR: **B**, systematic review of observational studies, single cohort study, and 2 case series). Higher preoperative body mass index (BMI) is associated with more patients losing weight than lower preoperative BMI (SOR: **C**, retrospective case series).

A 2013 systematic review analyzed 12 studies (1 cohort, 11 case series; N=2,737) assessing weight loss after total knee arthroplasty, total hip arthroplasty, or both procedures.[1] Average age of the patients in the studies ranged from 65 to 71 years; mean preoperative weight or BMI was not reported. The patients did not receive any specific weight loss interventions or advice after surgery.

The percentage of patients across the studies who lost weight at 1 year after surgery ranged from 14% to 49%. The definition of weight loss varied across the studies, ranging from the US Food and Drug Administration (FDA) definition of 5% body weight change to mean weight change from baseline. The review authors concluded that more patients appeared to have gained weight than lost weight. Ten of the studies failed to adequately control for confounding variables, 5 studies were at high risk of selection bias, and 3 studies were unclear as to selection bias.[1]

A prospective, multicenter cohort study in 2016 compared patients with osteoarthritis receiving total knee arthroplasty (n=140) with patients not undergoing surgery (n=697).[2] Mean patient age was 62 years and the mean preoperative BMI was 30 kg/m^2.

Over 72 months, the knee arthroplasty group gained an average of 0.19 kg while the control group lost an average of 0.76 kg, neither of which was statistically significant compared with their baseline or each other.[2]

A single-center, retrospective case series of patients who underwent total knee or total hip arthroplasty (N=6,929) reassessed patients' self-reported weight 2 years after surgery.[3] Patients were divided into obesity classes based on baseline BMI (normal=BMI 18.5–24.9 kg/m^2, overweight=BMI 25–29.9 kg/m^2, class 1=BMI 30–34.9 kg/m^2, class 2=BMI 35–39.9 kg/m^2, and class 3=BMI ≥40 kg/m^2) and a significant change in BMI was considered 5% in either direction.

Altogether, 71% of patients had no change in BMI after 2 years. Across obesity classes, 9% to 16% of patients had an increase in BMI. Considering class 1 through class 3 baseline BMI, an increasing percent of patients had a decrease in BMI: from 23% to 35% for hip and 24% to 33% for knee arthroplasty. Compared with patients who had normal BMI, patients in all obesity classes were more likely to have a >5% decrease in BMI: class 1 odds ratio (OR) 3.0 (95% CI, 2.1–4.3); class 2 OR 4.2 (95% CI, 2.8–6.4); and class 3 OR 5.3 (95% CI, 3.3–8.6).[3]

A prospective, single-institution case series in 2015 monitored weight change in 64 individuals undergoing total knee or hip arthroplasty.[4] Patients had a mean age of 68 years and preoperative BMI of 30 kg/m^2.

CONTINUED

Only 49 patients (20 hip and 29 knee patients) completed the required follow-up of 6 months. Five hip surgery patients (25%) and 11 knee surgery patients (38%) met the FDA criteria for weight loss (>5% body weight) by completion of the study.[4]

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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 Navy Medical Department, the Navy at large, or the Department of Defense.

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What ingestions warrant activated charcoal administration?

EVIDENCE-BASED ANSWER

Very few. Activated charcoal does not decrease the length of emergency department or hospital stay, mortality, vomiting, or intensive care unit (ICU) admission in patients with toxic ingestions (SOR: **B**, single unblinded RCT). Activated charcoal should not be administered routinely, but may be considered if a patient has ingested a potentially toxic amount of a poison known to be absorbed by charcoal, has ingested the substance within 1 hour of presentation, and has a patent or protected airway. Substances not absorbed by activated charcoal include hydrocarbons, acids, and alkalis (SOR: **C**, expert opinion).

A 2005 unblinded RCT examined 327 patients at least 16 years old who presented with a deliberate oral overdose to determine whether the routine use of activated charcoal has an effect on length of stay, vomiting, mortality, or ICU admission.[1] Exclusion criteria included late presenters (>12 hours), ingestions of drugs not absorbed by activated charcoal (hydrocarbons, acids, and alkalis), and serious ingestions as determined by the attending physician (which included large doses of tricyclic antidepressants, antineoplastic medications, aspirin, and cardioactive agents). The most common ingestions were benzodiazepines, paracetamol, and selective serotonin reuptake inhibitors.

More than 80% of the patients presented within 4 hours of ingestion and the results were similar when data from only early presenters (<2 hours, 57.8% of patients) were analyzed. No significant differences were noted between patients given activated charcoal or no gastrointestinal (GI) decontamination in terms of length of emergency department/hospital length of stay (activated charcoal 6.8 hours vs controls 5.5 hours; P=.11). There were also no significant differences between activated charcoal and no GI decontamination for the secondary outcomes of vomiting (activated charcoal 15% vs controls 14%; P=.88) or ICU admission (activated charcoal 5% vs controls 2%; P=.22). Only 1 death occurred: in the group with no GI decontamination in a patient later found to have ingested hydrocarbons who should have been excluded from the trial.[1]

That same year, the American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists published a position paper stating that no new evidence was available that would warrant any change to their 1997 position statement.[2] They maintained that there was no evidence that activated charcoal improves clinical outcome and recommended that activated charcoal not be administered routinely for the management of poisoned patients.

The position paper stated that administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison and the following criteria are met: ingested substance is known to be absorbed by charcoal, was ingested within 1 hour of presentation, and the airway is patent or protected.[2]

The authors noted that volunteer studies show decreased effectiveness of activated charcoal over time; mean amount of drug absorbed was 47%, 40%, 17%, and 21% when activated charcoal was administered versus no decontamination at 30, 60, 120, and 180 minutes after ingestion, respectively. The authors warned, however, that the potential for benefit with

decontamination after 1 hour of ingestion cannot be excluded given the lack of well-designed studies.[2]

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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 Air Force Medical Department, the Air Force at large, or the Department of Defense.

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In unfluoridated communities, is fluoride supplementation effective for reducing cavities?

EVIDENCE-BASED ANSWER

Oral fluoride supplementation reduces the incidence of permanent teeth dental caries in children in communities without water fluoridation by 24% to 29% (SOR: **A**, meta-analysis of RCTs). Topical fluoride treatment reduces the fraction of dental caries by 26% at 1 year regardless of water fluoridation status (SOR: **A**, meta-analysis of RCTs). Oral fluoride supplementation should be prescribed for children starting at 6 months of age whose water supply is deficient in fluoride. Fluoride varnish should be applied to the teeth of infant and children starting at the age of primary tooth eruption (SOR: **B**, expert opinion based on meta-analyses of RCTs).

A 2011 meta-analysis of 11 RCTs compared fluoride supplementation with no supplementation for the prevention of primary and permanent teeth dental caries among children aged ≤16 years, irrespective of background fluoride exposure.[1] Ten of the RCTs were conducted in communities without water fluoridation.

Patients (N=3,870) received fluoride supplementation in multiple oral forms (drops, tablets, solutions, or lozenges) with dosages ranging from 0.25 to 1 mg daily. Patients were followed for a minimum of 2 years. Dental caries were defined as decayed, missing, and filled teeth or teeth surfaces. Outcomes were measured as prevented fraction: mean dental caries in controls minus mean in treated group divided by mean in controls.[1]

Fluoride supplementation reduced dental caries in permanent tooth surfaces (3 trials, n=1,240; prevented fraction 0.24; 95% CI, 0.16–0.33) and in permanent teeth (3 trials, n=1,208; prevented fraction 0.29; 95% CI, 0.19–0.39). No effect was found on primary teeth. Bias was unclear in 10 studies, because of insufficient reporting of dropout rate.[1]

A 2003 meta-analysis of 133 RCTs involving patients aged ≤16 years (N=65,169) compared topical fluoride therapy with placebo (or no topical fluoride) for 1 year or school year.[2] Topical fluoride treatment included varnish, toothpaste, mouth rinse, gel, or any fluoride agent in any concentration, amount or duration, or technique of application; all studies needed to be continued at least 1 year. The change in decayed, missing, and filled tooth surfaces was measured and reported as the prevented fraction of caries.

The group receiving topical fluoride had a pooled prevented fraction estimate of 26% (95% CI, 24–29). No statistical difference was noted between groups with fluoridated water or lack thereof. The risk of bias was low.[2]

In 2014, the US Preventive Services Task Force (USPSTF) updated a 2004 recommendation statement on prevention of dental caries from birth through 5 years, based on a systematic evidence review including the 2 meta-analyses above.[3]

The USPSTF recommended prescribing oral fluoride supplementation for children starting at age 6 months whose water supply is deficient in fluoride (Grade: B, "high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial"). The Task Force recommended applying fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption (Grade: B).[3] EBP

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Does statin therapy improve morbidity or mortality in patients older than 65 years without diabetes or known cardiovascular disease?

Bottom line

There is no clear evidence that statin therapy improves either cardiovascular mortality or all-cause mortality in nondiabetic patients older than 65 years who do not have known heart disease. However, statins reduce myocardial infarction (MI) and possibly stroke, in a mixed population of diabetic and nondiabetic patients older than 65 years without existing cardiovascular disease (SOR: **B**, systematic reviews of RCTs with both diabetic and nondiabetic patients).

Evidence summary

A 2015 systematic review of 8 RCTs, including 25,952 patients older than 65 years, evaluated the effect of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, or rosuvastatin) versus placebo or usual care on primary prevention of MI, stroke, composite major adverse cardiovascular events (MI, stroke, revascularization, cardiac sudden death, or angina), and all-cause mortality.[1] Participants were a mean age of 73 years (range 69–76 years) and 51% had diabetes. Outcomes were measured over a mean follow-up of 3.5 years (range 1–5 years).

Pooled analyses showed no significant differences between groups in all-cause mortality (see TABLE). Statins reduced the risk of total MI by 26% and composite major adverse cardiovascular events by 18% over 3.5 years (see **TABLE**). No differences were noted in myalgia or hepatic transaminase elevations.[1]

A similar 2013 systematic review of 8 RCTs, including 24,674 patients older than 65 years, evaluated the effect of statins on primary prevention of MI, stroke, cardiovascular mortality, and overall mortality.[2] This review differed from the above review by the inclusion of 1 trial with predominantly nondiabetic men (n=1,416), and exclusion of another trial, which studied 2,592 patients (75% male) with diabetes. Patients' mean age was 73 years; 43% were female, and 22% had diabetes. Outcomes were measured over a mean of 3.5 years.

Pooled analysis found no differences in all-cause mortality or cardiovascular deaths between the groups (see **TABLE**).

TABLE

Effect of statin versus placebo therapy on primary cardiovascular prevention in predominantly nondiabetic patients aged >65 over 3.5 years[1,2]

Study	No. of RCTs	No. of patients	Outcome measured	RR (<1 favors statin)	95% CI	ARR	NNT
Savarese et al[2]	7	21,435	All-cause mortality	0.94	0.86–1.03	NS	NS
Teng et al[1]	7	23,360	All-cause mortality	0.96	0.88–1.04	NS	NS
Savarese et al[2]	5	13,914	Cardiovascular death	0.91	0.69–1.2	NS	NS
Teng et al[1]	7	18,914	Composite major adverse cardiovascular events[a]	0.82	0.74–0.92	NA	NA
Savarese et al[2]	5	15,929	MI	0.61	0.43–0.85	1.2%	83
Teng et al[1]	5	20,317	MI	0.74	0.61–0.9	1.3%	79
Savarese et al[2]	5	16,332	Stroke	0.76	0.63–0.93	0.7%	142
Teng et al[1]	5	16,436	Stroke	0.85	0.68–1.1	NS	NS

[a]Composite major adverse cardiovascular events include MI, stroke, revascularization, cardiac sudden death, or angina.

ARR=absolute risk reduction; CI=confidence interval; MI=myocardial infarction; NA=not available; NNT=number needed to treat (for 3.5 years); NS=nonsignificant result; RR=relative risk.

Statins reduced the relative risk of MI by 39% and stroke by 24% over the study period. Adverse events were not evaluated.[2]

The overall risk of bias of the 9 total studies included in the 2 systematic reviews was low, except for possible sponsorship bias. Of note, most of the trials included diabetic patients, and some were not initially designed to focus on the elderly.

Recommendations from others

The American Heart Association/American College of Cardiology (AHA/ACC) 2013 guidelines recommended that moderate- to high-intensity statin therapy be given to nondiabetic adults who meet the following criteria: 40 to 75 years old; serum low-density lipoprotein level of 70 to 189 mg/dL; no known atherosclerotic cardiovascular disease (ASCVD); and an estimated 10-year ASCVD risk >7.5% (AHA/ACC class 1, level of evidence A: treatment should be administered, based on data derived from multiple RCTs).[3] EBP

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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

WHO=World Health Organization

CONTINUED FROM PAGE 3

Recommendations from others

The 2009 evidence-based guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) recommended that ASA or NSAIDs be continued for all endoscopic procedures, and that clopidogrel should be withheld if polypectomy is a possibility.[2] The ASGE also recommended a cardiology or neurology consultation before stopping clopidogrel to optimize individual management. EBP

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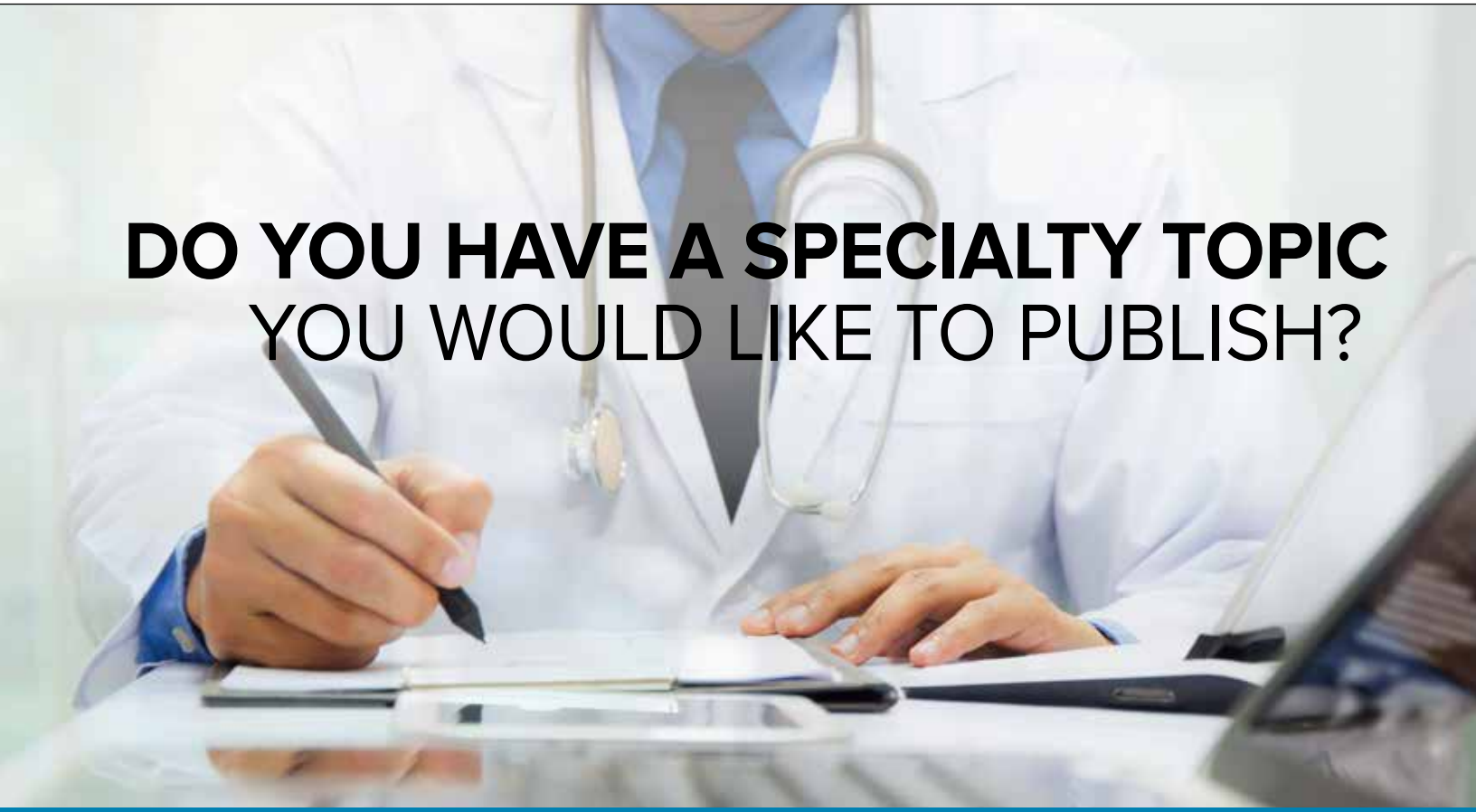

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ISSN 1095-4120 (print)
ISSN 2473-3717 (online)

Vol 20 | No. 8 | August 2017 | Electronic Version

EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

Are calcium channel blockers effective for treating primary Raynaud's phenomenon?

EVIDENCE-BASED ANSWER

As a drug class, calcium channel blockers (CCBs) are minimally effective for reducing the frequency of attacks of primary Raynaud's phenomenon (SOR: **A**, meta-analysis of RCTs) and reducing the severity of attacks by about 14% (SOR: **B**, meta-analysis of heterogenous RCTs). Nifedipine may be more effective than other agents in this class (SOR: **B**, consistent subanalyses within systematic reviews).

A 2014 meta-analysis included 7 randomized trials (6 crossover design, 1 parallel design) including a total of 358 adults with primary Raynaud's phenomenon, comparing CCBs with placebo over study periods of 2 weeks to 13 months.[1] CCBs included oral nifedipine 10 to 20 mg 3 times a day, nifedipine sustained release 30 to 60 mg daily, nicardipine 20 to 30 mg 3 times a day, and nicardipine long acting 50 mg twice a day.

Pooling the data, CCBs resulted in a small decrease in the frequency of attacks per week compared with placebo (7 trials, n=358; standardized mean difference [SMD] 0.23; 95% CI, 0.08–0.38). The authors calculated the difference in attacks per week to be 1.7 (95% CI, 0.6–2.8). Subanalysis of the nifedipine trials showed a small but statistically significant decrease in attacks compared with placebo (4 trials, n=206; SMD 0.32; 95% CI, 0.10–0.54), but subanalysis of the nicardipine trials showed no difference (3 trials, n=152; SMD 0.15; 95% CI, –0.06 to 0.35). The authors concluded that CCBs were minimally effective for reducing the frequency of attacks.[1]

A 2005 meta-analysis of 17 randomized trials (15 crossover design; 5 were also in the systematic review above) compared 4 oral CCBs with placebo in patients with primary Raynaud's to evaluate the change in number and severity of Raynaud's attacks.[2] CCBs included nifedipine 10 to 20 mg 3 times a day, nicardipine 20 mg 3 times a day or 50 mg extended-release daily, nisoldipine 10 or 20 mg daily, or diltiazem 120 mg 3 times a day. Outcomes were change in frequency of attacks per week and severity of attacks on a 0- to 10-cm visual analog scale.

CCBs provided a reduction in the frequency of ischemic attacks over a 1-week time period compared with placebo (17 trials, n=348; weighted mean difference [WMD] –5; 95% CI, –9 to –0.99). When 2 trials were removed from the calculation because of heterogeneity, the result was still statistically significant (15 trials, n=332; WMD –2.8; 95% CI, –3.9 to –1.7). CCBs also decreased the severity of attacks (8 trials, n=294; WMD –1.4; 95% CI, –2.2 to –0.58). In a subanalysis of 12 trials (n=252), nifedipine significantly reduced the frequency of ischemic attacks (WMD –6.1 per week; 95% CI, –11.2 to –0.19) and decreased the severity of attacks (WMD –1.8; 95% CI, –32.1 to –0.54). Subanalysis of nicardipine and nisoldipine showed no reduction in frequency or severity of ischemic attacks compared with placebo. The meta-analysis was limited overall by a small number of studies meeting inclusion criteria, small sample sizes, subjective outcome measurements, and heterogeneity between the trials (χ^2=263, df=16, P<.00001).[2]

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How effective is continuous glucose monitoring in patients with type 1 diabetes?

EVIDENCE-BASED ANSWER

In adults, continuous glucose monitoring used with pump-delivered insulin (PDI) or as part of an integrated, continuous monitor-in-pump delivered insulin (IPDI) system reduces glycated hemoglobin (HbA1C) 0.29 to 1.1 points more than self-monitoring of blood glucose with multiple daily injections of insulin (MDI). In young adults, continuous monitoring is no different from self-monitoring for lowering HbA1C. In children, continuous monitoring with PDI or IPDI lowers HbA1C by 0.24 points more than self-monitoring with MDI at 3 months (SOR: **C**, meta-analysis of RCTs with disease-oriented evidence). Use of continuous monitoring to lower HbA1C is supported in adults and may be helpful in children (SOR: **C**, expert opinion).

A 2012 systematic review of 22 RCTs (N=2,883 children and adults) examined whether continuous monitoring compared with self-monitoring at least once a day improved HbA1C levels over 3 to 18 months in patients with type 1 diabetes.[1] Insulin was administered by MDI, PDI, or IPDI.

A subset of trials in children and adults, 1 to 70 years old, compared continuous monitoring with PDI or IPDI to self-monitoring with MDI. After 6 months, continuous monitoring and PDI led to slightly greater decrease in HbA1C than self-monitoring and MDI (6 trials, n=963; mean difference [MD] –0.52; 95% CI, –0.72 to –0.32). Continuous monitoring with IPDI compared to self-monitoring and MDI also led to slightly lower HbA1C after 6 months (2 trials, n=562; MD –0.68; 95% CI, –0.82 to –0.54). These changes in HbA1C persisted at 12 months with continuous monitoring and IPDI versus self-monitoring and MDI (1 trial, n=485; MD –0.60; 95% CI, –0.75 to –0.45).[1]

Three RCTs in this systematic review examined combinations of continuous monitoring with IPDI or PDI compared to self-monitoring and MDI in adult men and nonpregnant women older than 24 years old for 3 to 12 months. In 1 RCT (n=77) continuous monitoring and PDI compared to self-monitoring and MDI showed a greater reduction in HbA1C at 3 months (MD –1.1; 95% CI, –1.5 to –0.75) and 6 months (MD –1.1; 95% CI, –1.5 to –0.74). Another RCT (n=98) comparing continuous monitoring with IPDI or PDI to self-monitoring and MDI also showed greater reduction in HbA1C at 3 months (MD –0.29; 95% CI, –0.48 to –0.1) and 6 months (MD –0.52; 95% CI, –0.72 to –0.32). In a 12-month RCT (n=166), continuous monitoring with IPDI lowered HbA1C more than self-monitoring and MDI (MD –0.60; 95% CI, –0.76 to –0.44). In young adults 15 to 23 years old, both RCTs in this systematic review that examined continuous monitoring with IPDI or PDI with self-monitoring and PDI found no difference in HbA1C at 3 or 6 months.[1]

Four RCTs in the systematic review examined continuous monitoring and self-monitoring in various combinations with IPDI, PDI, and MDI in children younger than 15 years. In 1 RCT (n=114), continuous monitoring with IPDI or PDI showed a slightly greater decrease in HbA1C than self-monitoring and MDI at 3 months (MD –0.24; 95% CI, –0.47 to –0.01), but no difference at 6 months. Other comparisons of continuous monitoring with IPDI to self-monitoring and PDI or MDI showed no difference at 6 or 12 months.[1]

The validity of this review was limited by significant heterogeneity in age, baseline HbA1C, method of insulin delivery, and type of continuous monitor used in each study. All studies were sponsored by the monitor manufacturer, with 6 stating no conflict of interest.[1]

The 2015 American Diabetes Association standards of medical care in diabetes supports the use of continuous monitoring with intensive insulin regimens to lower HbA1C in adults aged ≥25 years (Level of evidence: A, based on RCTs).[2]

Continuous monitoring in children, teens, and younger adults may be helpful (Level of evidence: B, based on cohort studies). Proper use of the monitor, patient education, and ongoing support may improve success with continuous monitoring for all age groups.[2]

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What office-based interventions are effective for treating abnormal glucose levels or preventing progression to type 2 diabetes?

EVIDENCE-BASED ANSWER

Telemedicine interventions—including telephone and Internet-based monitoring and education—result in a slight reduction in glycated hemoglobin (HbA1C) in patients with diabetes (SOR: **C**, meta-analysis of RCTs with disease-oriented outcomes). In patients at risk for diabetes, an intensive lifestyle-based intervention that includes case managers, education, and other individualized forms of support reduces the incidence of diabetes by 58% over 3 years (with continued but less effect over 15 years), reduces the prevalence of microvascular disease among women, and is superior to metformin alone (SOR: **B**, RCT and large cohort study).

A 2014 systematic review and meta-analysis reviewed 35 RCTs (N=6,921) comparing telemedicine-based interventions with standard care for diabetic control.[1] Patient mean ages were 43 to 71 years and 42 to 71 years in the intervention and control groups, respectively, with treatment duration ranging from 3 to 60 months. Patients had type 2 diabetes, and received either insulin or oral diabetic medications. Primary outcomes were HbA1C pre- and postintervention, and cost effectiveness.[1]

Twelve trials used telephone-based interventions through periodic conversation or text messaging. Nineteen trials used Internet-based interventions in which participants uploaded blood glucose readings manually or electronically, with follow-up via videoconferencing or telephone. Four trials used Internet-transmitted interventions, directly transmitting participant blood glucose data to the provider's office via Internet, telephone, or other remote devices.

Results showed a slight reduction in HbA1C in the telemedicine groups compared with the controls (mean difference [MD] –0.37; –95% CI, –0.49 to –0.25).[1]

A 2002 RCT of 3,234 nondiabetic US adults (mean age 51 years) compared treatment with an intensive lifestyle-modification program (n=1,079), metformin 850 mg twice daily (n=1,073), or placebo (n=1,082).[2] The intensive lifestyle-modification program included individual case managers, frequent contact, lifestyle education classes, supervised physical activity, flexible maintenance interventions, individualized adherence strategies, strategies to address ethnic diversity, and a network of training, feedback, and clinical support. All patients had elevated fasting (95–125 mg/dL) and 2-hour post 75-g glucose load (140–199 mg/dL) plasma glucose concentrations. The average follow-up was 2.8 years and the primary outcome was incidence of diabetes, defined as fasting glucose ≥126 mg/dL, or blood glucose ≥200 mg/dL 2 hours after a 75-g glucose load.

The incidence of diabetes at the end of the study period was 4.8, 7.8, and 11.0 cases per 100 person-years in the lifestyle, metformin, and placebo groups, respectively. Lifestyle intervention and metformin reduced the incidence of diabetes by 58% (95% CI, 0.48–0.66; number needed to treat [NNT]=7) and 31% (95% CI, 0.17–0.43; NNT=14), respectively, compared with placebo. Lifestyle intervention reduced diabetes incidence by 39% (95% CI, 0.24–0.51) compared with metformin.[2]

From 2002 to 2014, 2,776 of the patients (mean age 66 years) from the above RCT were monitored in an intention-to-treat analysis to study long-term effects of lifestyle intervention (n=915) and metformin (n=926) compared with control (n=935).[3] The primary outcomes were diabetes incidence and the prevalence of microvascular disease defined as nephropathy, retinopathy, and neuropathy. After completion of the initial study above, all patients were unblinded and offered lifestyle training with quarterly maintenance group lifestyle sessions for 1 year.

Starting in 2002, the group originally randomized to metformin therapy continued to receive metformin 850 mg twice daily (unmasked), and patients who had originally been in the lifestyle intervention group were offered biannual supplementary group programs, reinforcing behavioral self-management activities, with an individual lifestyle check-in. There was no placebo given in the follow-up period and patients were analyzed according to their assigned group in the original study period.[3]

During a mean follow-up of 15 years, diabetes incidence was reduced 27% in the lifestyle intervention group (hazard ratio [HR] 0.73; 95% CI, 0.65–0.83) and 18% in the metformin group (HR 0.82; 95% CI, 0.72–0.93) compared with the control group. The differences between groups declined over time;

by the end of the follow-up period, the cumulative diabetes incidence was 55% in the lifestyle intervention group, 56% in the metformin group, and 62% in the control group. No differences were noted in microvascular disease prevalence among the groups, except among women in whom lifestyle interventions reduced prevalence by 21% (RR 0.79; 95% CI, 0.64–0.98) compared with placebo and by 22% (RR 0.78; 95% CI, 0.62–0.96) compared with metformin.[3]

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Are intranasal steroids effective for symptomatic treatment of patients with sinus congestion?

EVIDENCE-BASED ANSWER

In acute sinusitis, intranasal steroids resolve or improve symptoms slightly better than placebo, with higher doses more effective than lower doses (SOR: **A**, meta-analysis of RCTs). In acute rhinosinusitis, fluticasone intranasal spray once or twice daily improves symptom scores slightly more than placebo (SOR: **B**, single RCT). Intranasal steroids are an option for viral rhinosinusitis and acute bacterial rhinosinusitis and recommended for chronic rhinosinusitis (SOR: **B**, evidence-based guideline).

In a 2013 meta-analysis of 4 RCTs of 1,943 adults and children compared intranasal mometasone or fluticasone with placebo for symptom improvement or resolution in acute sinusitis.[1] Doses were converted to mometasone equivalents of 200, 400, or 800 µg total daily doses. Patients were 12 to 76 years old with mild to moderate sinusitis confirmed by radiology or nasal endoscopy, excluding fulminant bacterial rhinosinusitis, chronic sinusitis, or recent nasal/sinus surgery.

Pooled results for all intranasal steroid doses showed that more patients receiving intranasal steroid had resolution or improvement of symptoms compared with placebo, but definition of improvement and symptom scales used were not specifically reported (3 trials, n=1,792; relative risk [RR] 1.1; 95% CI, 1.0–1.2; number needed to treat [NNT]=16).[1]

In subgroup analysis, the 400-µg dose was found to be beneficial (2 trials, n=1,130; RR 1.1; 95% CI, 1.0–1.2; NNT=17); however, the 200-µg dose was no different from placebo (2 trials, n=590; RR 1.0, 95% CI, 0.98–1.1). Only 1 study evaluated the 800-µg dose for resolution or improvement of symptoms; a statistically significant effect was noted (1 trial, n=324; RR 1.2; 95% CI, 1.1–1.4).[1]

In 2012, a randomized, double-blind, parallel-group study (67 sites in 12 countries; N=724) compared fluticasone furoate nasal spray (110 µg once or twice daily) with placebo for reduction of symptoms of uncomplicated acute rhinosinusitis.[2] Patients were adolescents and adults with symptoms of rhinosinusitis for 5 to 8 days, excluding fulminant bacterial rhinosinusitis, chronic/recurrent rhinosinusitis, or allergic rhinitis. Symptoms were measured twice daily using the major symptoms score (MSS), which consisted of questions assessing nasal congestion/stuffiness, sinus headache/sinus pressure, and postnasal drip on a 0 to 3 scale; a maximum score of 9 would indicate worse symptoms. Patients were treated for a 2-week period with an additional 2-week follow-up.

Daily use of fluticasone nasal spray reduced the MSS by 3.4 points, slightly better than the 3.0 points with placebo (mean difference [MD] –0.39; 95% CI, –0.6 to –0.10) while twice-daily fluticasone reduced MSS by 3.3 points (MD –0.36; 95% CI, –0.64 to –0.07).[2]

In 2015, the American Academy of Otolaryngology-Head and Neck Surgery updated their 2007 evidence-based practice guideline for adult sinusitis with a systematic review of 42 systematic reviews, 5 practice guidelines, and 70 RCTs.[3] The guideline assessed the effectiveness of analgesics, NSAIDs, saline nasal irrigation, decongestants, antihistamines, systemic steroids, and intranasal steroids in adults with viral rhinosinusitis (VRS), acute bacterial rhinosinusitis (ABRS), and chronic rhinosinusitis (CRS).

The proportion of patients with symptom improvement was slightly greater with intranasal steroids versus placebo

for VRS (6 trials, n=2,495; 73% vs 66%; RR 1.1; 95% CI, 1.0–1.2); ABRS (4 trials, n=1,792; RR 1.1; 95% CI, 1.0–1.2); and CRS (10 trials, n=2,495; RR 1.1; 95% CI, 1.2–2.4). The guideline stated that intranasal steroids may be considered for VRS (guideline level of evidence [LOE] B: systematic review of RCTs with unclear balance of benefit and harm) and ABRS (LOE A: systematic review of RCTs) and recommended them for CRS (LOE A: systematic review of RCTs).[3]

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Do inhaled beta-agonists control cough in acute bronchitis?

EVIDENCE-BASED ANSWER

Maybe. Pooled evidence from RCTs reveals no reduction in productive cough with use of beta-2-agonists (SOR: **B**, meta-analysis of 2 small RCTs). When the RCTs were evaluated separately, albuterol led to a 30% absolute decrease in cough at 7 days but had no effect on nighttime cough or productive cough. Fenoterol reduced productive cough but not total daytime or nighttime cough (SOR: **C**, small RCTs).

A 2015 systematic review (7 RCTs, N=552) examined the effects of inhaled or oral beta-2-agonists compared with placebo on acute cough in patients with a clinical diagnosis of acute bronchitis.[1] The review identified 2 RCTs (n=119) that compared the inhaled beta-2-agonists albuterol (dose not specified) and fenoterol (0.2 mg 4 times a day) with placebo. Adults older than 18 years were included and individuals with preexisting pulmonary disease or another acute respiratory illness were excluded.

In the only outcome that could be pooled in the 2 trials, no significant difference was noted in the presence of a productive cough after 7 days (relative risk [RR] 0.76; 95% CI, 0.32–1.8).[1]

The RCT evaluating inhaled albuterol in the systematic review compared the effect of inhaled albuterol using a metered-dose inhaler (MDI) with a placebo inhaler with or without erythromycin 250 mg tablets (regimen not specified) on cough at 7 days.[2] The study enrolled adult patients aged 18 to 65 years without a history of asthma or chronic obstructive pulmonary disease (n=46) who presented with a productive cough of <30 days' duration and had no signs of pneumonia. Patients were randomized to albuterol (dose not given) with erythromycin, albuterol with placebo tablet, erythromycin with placebo inhaler, or 2 placebos. No significant differences were noted in patient demographics among the groups with regard to age, sex, and cigarette use.

After 7 days, albuterol inhaler, with or without erythromycin, compared with placebo inhaler, with or without erythromycin, decreased the percentage of patients still coughing (61% vs 91%; *P*=.02). However, no difference was noted in the percentage of patients with a productive cough (57% vs 48%; *P* not significant) or persistent night cough (26% vs 45%; *P* not significant). Inhaler technique or use of spacers was not described in this study and could contribute to inconsistent dosing.[2]

The RCT evaluating inhaled fenoterol in the systematic review enrolled 73 patients aged 18 to 65 years who presented with cough or dyspnea after 10 days of acute bronchitis.[3] Patients were excluded if they had been treated with antibiotics within the last 3 days or if they had other possible causes of cough. Patients were randomized to inhaled fenoterol 0.2 mg or inhaled placebo 4 times daily. Outcomes at 7 days included patients' self-assessed and self-reported symptoms of daytime cough, productive cough, and nighttime cough. Each symptom was assessed on a scale from 0 to 2 as follows: 0, symptoms not present or present as usual; 1, symptom is more annoying than normal; 2, symptom is very annoying.

No difference was noted between fenoterol and placebo in percent reduction of symptom score from baseline to day 7 for the symptoms of daytime cough (–62% vs –43%; *P*=.1) or nighttime cough (–76% vs –70%; *P*=.62). Fenoterol had a greater percent reduction in productive cough (–64% vs –33%; *P*=.03). Limitations of this study include the disparate

use of antibiotics (40%) in the fenoterol group versus the placebo group (28%); also, spacer devices were not used in this trial, resulting in a greater potential for suboptimal or inconsistent dosing.[3]

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Does fluoridated water decrease dental caries in children?

EVIDENCE-BASED ANSWER

Yes, community water fluoridation is associated with a 26% to 35% decrease in dental caries in children, but is also associated with a 12% incidence of esthetically displeasing fluorosis stains (SOR: **B**, systematic review of observational studies at high risk of bias). The US Public Health Service and several medical and dental specialty societies recommend community water fluoridation to prevent dental caries (SOR: **C**, expert opinion).

A 2015 systematic review of 107 prospective observational studies (total N not provided) evaluated community water fluoridation for preventing dental caries in children.[1] Nineteen of the studies compared children 3 to 15 years old exposed to water fluoridation at "optimal" levels (0.6–1.2 parts per million [ppm]) with children exposed to "natural" or "low" levels (<0.35 ppm) and reported dental health outcomes after a range of follow-up times (3–20 years). The reviewers defined dental health outcomes either as the change in the number of decayed, missing, or filled teeth, or as a percent of caries-free children. In the individual studies these outcomes were measured by dental examiners (unspecified training or blinding) evaluating either radiographs (1 study) or participants' dental examinations.

When compared with low or natural fluoride levels, community water fluoridation resulted in a 35% (deciduous teeth) and 26% (permanent teeth) reduction in the average number of decayed, missing, or filled teeth (see **TABLE**). Other findings included a 15% increase in the proportion of children with no dental caries for children with deciduous teeth (10 studies, n=19,983; 95% CI, 0.11–0.19) and 14% increase for children with permanent teeth (8 studies, n=26,769; 95% CI, 0.05–0.23).[1]

Water fluoridation was also associated with a nearly 3-fold higher odds of dental fluorosis of esthetic concern for each 1 ppm increase in fluoride (40 studies, n=59,630; odds ratio 2.9; 95% CI, 2.1–4.1). The authors calculated that in areas with a water fluoride level of at least 0.7 ppm, approximately 12% of people evaluated had fluorosis that could cause concern about their appearance.[1]

Overall, the reviewers deemed these observational studies at high risk for bias due to confounding and lack of adjustment for risk factors, incomplete outcome data, and lack of blinding of outcome assessors. Other limitations included the lack of any RCTs as well as a lack of evidence reflecting changes in fluoride availability from other sources. Of note, 17 of 20 studies were done prior to the widespread introduction of fluoride-containing toothpaste in the late 1970s.[1]

The US Public Health Service recommends an optimal fluoride concentration of 0.7 ppm, which reflects a balance

TABLE

Summary of the effect of water fluoridation on the mean difference in decayed, missing, or filled teeth (DMFT)[1]

Type of teeth	No. of studies (no. of participants)	Median no. of DMFT in area with low/ nonfluoridated water	Mean decrease in no. of DMFT in area with fluoridated water	95% CI
Deciduous	9 studies (22,134)	5.1	1.8 (35% fewer)	1.3–2.3
Permanent	10 studies (39,382)	4.4	1.2 (26% fewer)	0.72–1.6

of providing protection from dental caries and limiting dental fluorosis.[2]

The American Academy of Pediatrics' statement based on group consensus recommends community water fluoridation as a cost-effective intervention for the prevention of dental caries for pre- and posteruptive teeth that cannot be predictably found in bottled water.[3]

The American Academy of Family Physicians endorses community water fluoridation for prevention of dental caries in both children and adults, based on high-quality evidence from systematic reviews.[4] The American Dental Association endorses community water fluoridation as safe, effective, and necessary in preventing tooth decay.[5]

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What is the best clinical scale to diagnose major depressive disorder in patients with dementia?

EVIDENCE-BASED ANSWER

The available options are only somewhat useful. The Cornell Scale for Depression in Dementia (CSDD) is only marginally sensitive for diagnosing depression in patients with dementia, with a positive likelihood ratio (LR+) of 1.6. The Geriatric Depression Scale (GDS-30) correlates moderately with the CSDD in patients with mild cognitive impairment but only weakly in patients with Alzheimer's dementia (SOR: **B**, prospective cohort studies).

A 2015 cross-sectional study (N=92) performed in 14 Australian nursing homes assessed the nursing staff's ability to complete the CSDD to screen for depression in patients with and without dementia.[1] The CSDD consists of 19 patient and informant interview questions (total score=38 points, <6 points implies no depressive symptoms). The gold standard for a diagnosis of depression in individuals with dementia was made by blinded specialist clinicians who used the Provisional Diagnostic Criteria for Depression in Alzheimer's.

Dementia was suspected, based on answers to the Mini-Mental Status Examination and the Global Deterioration Rating Scale, in 50% (n=46) of the 92 patients and 28% (13 of 46) of these patients had depression. Nursing home staff administered the CSDD and a score of 10 or higher was used to diagnose depression. In patients with dementia, the CSDD had a sensitivity and specificity of 69% and 57%, respectively, with a LR+ of 1.6 (95% CI, 1.1–2.4) and a negative likelihood ratio (LR¬–) of 0.54 (95% CI, 0.26–1.2). Limitations of the study included a small sample size and use of a high CSDD cutoff score.[1]

A 2014 cross-sectional study of 242 patients with memory problems referred to a United Kingdom memory clinic evaluated the CSDD in patients with or without dementia and with or without depression.[2] Mean patient age was 70 years (range 37–97 years) and 48% were women. Based on the DSM IV clinical diagnostic criteria (gold standard), 98 (40.5%) of the patients had dementia, 32 (13.2%) had depression, and 9 (3.7%) had depression with dementia.

For the entire cohort, the mean CSDD score was 12.6 in patients diagnosed with depression and 3.2 in patients without depression ($P<.001$). The mean CSDD was 3.2 in patients diagnosed with dementia and 5.3 in patients without dementia ($P<.01$). Performance of the CSDD in patients with both dementia and depression versus patients without either dementia or depression was not reported. The study was limited by a low prevalence of depression, especially in patients with dementia.[2]

A 2009 prospective cohort study of 403 adults (age range 49–98 years) in a memory clinic evaluated the GDS-30 as a screening tool for depression in mild cognitive impairment and Alzheimer's dementia, using the CSDD as the gold standard.[3] Depression was defined as a CSDD score of 8 or higher. Mild cognitive impairment and Alzheimer's disease were diagnosed based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria. The GDS-30 is a validated 30-item self-rating scale

for depression screening in elderly people without cognitive impairment.

In patients with mild cognitive impairment, the GDS-30 moderately correlated with the CSDD (Pearson's r=0.57; *P*<.001) and a GDS-30 cutoff score of 8 or higher was 95% sensitive and 67% specific for diagnosing depression (LR+ 2.9; 95% CI, 2.2–3.7; LR– 0.07; 95% CI, 0.01–0.5). In patients with Alzheimer's dementia, the GDS-30 scores only weakly correlated with CSDD scores (Pearson's r=0.31; *P*<.001) and sensitivity and specificity were not reported. A limitation of this study was the use of the CSDD as the gold standard.[3]

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In patients with diabetes, are clopidogrel and ticlopidine effective for primary and secondary prevention of cardiovascular disease?

EVIDENCE-BASED ANSWER

In patients with diabetes and cardiovascular disease (CVD), adenosine diphosphate (ADP) receptor antagonists (ticlopidine and clopidogrel) do not reduce all-cause mortality, vascular mortality, or myocardial infarction (MI) compared with placebo (SOR: **B**, individual RCT). In patients with diabetes and CVD or CVD risk factors, ADP receptor antagonists, alone or in combination with aspirin, do not reduce the combined risk of stroke, MI, and vascular mortality more than aspirin alone (SOR: **B**, individual RCTs).

In a 2012 systematic review of 8 RCTs including 21,379 patients with type 2 diabetes and a history of CVD (mostly stroke or coronary disease), compared ADP receptor antagonists with placebo or other antiplatelet (aspirin and dipyridamole) agents to assess their effect on all-cause mortality, stroke, and MI over 1 to 2.5 years.[1] Only 3 trials had data on 1 of the primary outcomes for diabetic patients.

In 1 trial (n=335) ticlopidine (250 mg twice daily) compared with placebo did not reduce vascular mortality (odds ratio [OR] 0.94; 95% CI, 0.47–1.9), all-cause mortality (relative risk [RR] 1.3; 95% CI, 0.71–2.3), or MI (RR 0.78; 95% CI, 0.39–1.6). Clopidogrel (75 mg daily) or ticlopidine were no better than other antiplatelets (aspirin and dipyridamole) for reducing nonfatal and fatal stroke (2 RCTs, n=6,340; OR 0.81; 95% CI, 0.44–1.5).[1]

A 2006 multicenter, double-blind RCT (1 of the 5 other trials in the systematic review above) of 15,603 patients (including 6,556 patients with diabetes, median age 64 years) examined the effect of clopidogrel (75 mg daily) plus low-dose aspirin (75–162 mg daily) (n=7,802) or placebo plus low-dose aspirin (n=7,801) on combined outcome of MI, stroke, or death from cardiovascular causes.[2] Patients had clinically evident CVD or multiple atherothrombotic risk factors including diabetes, diabetic nephropathy, ankle/brachial index <0.9, asymptomatic carotid disease, hypercholesterolemia, current smokers, or male sex.

In a subgroup analysis of diabetic patients, clopidogrel plus low-dose aspirin compared with placebo plus aspirin did not reduce the combined outcome.[2]

A 2003 multicenter RCT (also 1 of the 5 other studies in the systematic review above) with a 2-year follow-up compared ticlopidine 250 mg twice daily plus placebo with aspirin 325 mg twice daily plus placebo in 1,809 black men and women (including 738 patients with type 1 and type 2 diabetes) with a history of a previous noncardioembolic ischemic stroke.[3] No statistically significant difference was found in the combined outcome of recurrent stroke, MI, or vascular death in all patients, including patients with diabetes.

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Is a Mediterranean diet effective for decreasing rates of nonfatal and fatal cardiac events in adults with low cardiovascular risk versus a normal diet?

EVIDENCE-BASED ANSWER

Adherence to a Mediterranean diet is associated with decreased rates of fatal and nonfatal cardiac events in adults without cardiovascular disease at baseline (SOR: **B**, meta-analysis of cohort studies and subsequent cohort study). Increasing intake of only fruits, vegetables, and cereals has no effect on cardiovascular events in women (SOR: **B**, single RCT).

A meta-analysis of 18 cohort studies reviewed the association of Mediterranean diet with health outcomes (cardiovascular, cancer, and neurodegenerative disease incidence or mortality, and overall mortality) in nearly 2.2 million patients 20 to 95 years old without prior cardiovascular, neoplastic, or neurodegenerative disease.[1] A Mediterranean diet was defined as high consumption of fruits, vegetables, legumes, and complex carbohydrates; moderate consumption of fish; low to moderate amount of red wine during meals; and olive oil as the main fat source.

Studies had 4 to 20 years of follow-up and were adjusted for confounders (demographic, anthropometric, and traditional risk factors). The Mediterranean Diet Score (MDS) was used to evaluate patients' diets, with 1 point assigned for appropriate consumption of each of 9 items: legumes, whole-grain/cereals, fruits, vegetables, fish, unsaturated fats, alcohol, meat/poultry, and dairy.[1]

A 2-point increase in MDS was associated with a 10% reduction in cardiovascular incidence or mortality (7 studies, n=534,064; relative risk 0.90; 95% CI, 0.87–0.93).[1]

A subsequent Dutch cohort study of 34,708 adults 20 to 70 years old without cardiovascular disease or diabetes evaluated the incidence of fatal and total cardiovascular events in relation to the 9-point MDS over 12 years.[2] After adjusting for confounders (age, sex, smoking, physical activity, total energy intake, and educational level), a 2-point increase in MDS was associated with a 22% reduction of fatal cardiovascular events (hazard ratio [HR] 0.78; 95% CI, 0.69–0.88), a 5% reduction of total cardiovascular events (HR 0.95; 95% CI, 0.91–0.98), and a 15% reduction of composite cardiovascular events that included fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke (HR 0.85; 95% CI, 0.80–0.91).

A 2013 systematic review of 11 RCTs compared the effects of a Mediterranean-style dietary pattern on the primary prevention of cardiovascular events and its associated risk factors in 52,044 healthy adults aged 18 and older from the general population and those with high cardiovascular risk.[3] A Mediterranean dietary pattern was defined similarly to the Mediterranean diet above.

The trials were heterogeneous in the patients studied, follow-up duration, and the number of components relevant to a Mediterranean dietary pattern (only 7 trials described the intervention as a Mediterranean diet). Most trials focused on intermediate outcomes (such as blood pressure and lipid levels).[3]

Clinical events were reported in only 1 trial involving 48,835 postmenopausal women. However, the intervention in that trial was not described as a Mediterranean diet but as increased fruit, vegetable, and cereal intake. There were no significant effects of the intervention diet on fatal or nonfatal cardiovascular events at 8 years (HR 0.96; 95% CI, 0.89–1.0).[3]

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Are there any antenatal interventions that reduce trauma during vaginal delivery?

EVIDENCE-BASED ANSWER

Antenatal perineal massage decreases risk of perineal trauma and episiotomies in primiparous but not multiparous women (SOR: **A**, meta-analysis of RCTs). Using warm compresses and perineal massage during second stage of labor reduces the risk of third- and fourth-degree perineal lacerations (SOR: **A**, meta-analysis of RCTs). Perineal injection of hyaluronidase at the onset of the second stage of labor does not appear to prevent perineal trauma (SOR: **A**, meta-analysis of RCTs).

A 2013 meta-analysis of 4 RCTs (N=2,480) assessed perineal trauma after vaginal delivery in women who performed antenatal digital perineal massage versus no massage.[1] Digital perineal massage included the woman or her partner pressing downward and sideward or a sweeping motion with 1 or 2 fingers inserted 3 to 5 cm into the vagina every 1 to 2 days for 4 to 10 minutes, starting 4 or more weeks before delivery. All studies used sweet almond oil as coating for the fingers during massage.

Among primiparous women (n=1,988), perineal massage had a lower risk of trauma requiring suturing (risk ratio [RR] 0.9; 95% CI, 0.8–1.0; number needed to treat to benefit [NNTB]=14) and a lower risk of episiotomy (RR 0.8; 95% CI, 0.7–1.0; NNTB=18) than no massage. For multiparous patients, no difference was noted between perineal massage and no massage for trauma requiring suturing and need for episiotomy. No difference was noted for first- or second-degree perineal tears or third-/fourth-degree perineal trauma for any parity.[1]

A 2011 meta-analysis of 8 RCTs (N=11,651) compared various perineal techniques used during the second stage of labor versus no intervention for the outcome of perineal trauma (third- or fourth-degree tears and episiotomies) or intact perineum in singleton vaginal deliveries at term.[2] Perineal techniques included hands off (no touching of the perineum until the infant's head was crowning), warm compresses held to the perineum and external genitalia during and between pushes, and 2 finger perineal massage inside the vagina.

Use of warm compresses and perineal massage during the second stage of labor reduced the risk of third- or fourth-degree tears, but not episiotomy or intact perineum. Hands off technique reduced the risk of episiotomy and showed no significant difference in risk of intact perineum or third- or fourth-degree tears (see **TABLE**). The analysis was limited by significant heterogeneity.[2]

A 2014 meta-analysis of 4 RCTs (N=595) compared perineal hyaluronidase (HAase) injection (750–2,000 turbid-reducing units HAase) at the onset of the second stage of labor with perineal placebo injection (5 mL sterile normal saline) or no intervention for the outcomes of episiotomy, first- or second-degree tears, and third- or fourth-degree tears in singleton vaginal deliveries.[3]

TABLE

Comparison of outcomes after perineal interventions vs no intervention during second stage of labor[2]

Intervention	No. of trials (N)	Relative risk (95% CI) of		
		Intact perineum	Episiotomy	Third-/fourth-degree tears
Hands off	2 (6,547)	1.0 (0.95–1.1)	0.69[a] (0.50–0.96)	0.73 (0.21–2.6)
Warm compress	2 (1,525)	1.1 (0.86–1.3)	0.93 (0.62–1.4)	0.48[a] (0.28–0.84)
Perineal massage	2 (2,147)	1.0 (0.90–1.2)	1.4 (0.42–4.9)	0.5[a] (0.29–0.94)

[a]Statistically significant.

There was a lower risk of the composite endpoint of any perineal trauma in women who received HAase injections compared with the control combination of placebo injection and no intervention (RR 0.7; 95% CI, 0.5–1.0), but no difference in the risk of episiotomy (RR 0.7; 95% CI, 0.4–1.3), first- and second-degree perineal tears (RR 0.7; 95% CI, 0.4–1.3), or third- and fourth-degree tears (RR 0.1; 95% CI, 0.01–2.1). Two of the 4 studies included in the analysis contributed to high heterogeneity (I2=82%) within the meta-analysis; a subgroup analysis excluding those 2 RCTs resolved the heterogeneity (I2=7%) and showed no difference between HAase injection versus placebo injection for perineal trauma (RR 0.9; 95% CI, 0.8–1.1). EBP

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Empagliflozin for renal protection

Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016; 375(4):323–334.

In an RCT, which initially evaluated the cardiovascular outcomes of empagliflozin in 7,020 patients with type 2 diabetes mellitus, this secondary analysis examined the effects of renal microvascular outcomes.

In addition to standard care, patients were randomly assigned to receive oral empagliflozin 10 mg or 25 mg or placebo. Renal microvascular outcomes were defined as worsening nephropathy (progression to microalbuminuria), doubling of serum creatinine levels, progression to an estimated glomerular filtration rate (eGFr) <45 mL/min/1.73m^2, and progression to renal replacement therapy.

Over a median observation of 3 years, the empagliflozin group had a decreased risk of incident or worsening nephropathy (13% vs 19%; hazard ratio [HR] 0.61; 95% CI, 0.55–0.69), doubling of serum creatinine levels (1.5% vs 2.6%; HR 0.56; 95% CI, 0.39–0.79), and initiation of renal replacement therapy (0.3% vs 0.6%; HR 0.45; 95% CI, 0.21–0.97) compared with placebo. Adverse outcomes such as urinary tract infections, pyelonephritis, and hypoglycemia were similar in both groups.

In the original trial, at 1 year, the glycated hemoglobin (HbA1C) levels were significantly lower in the empagliflozin 10-mg group (mean difference [MD] –0.24 percentage points; 95% CI, –0.40 to –0.08) and 25-mg group (MD –0.36 percentage points; 95% CI, –0.51 to –0.20) compared with placebo.

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

Bottom line: The use of empagliflozin appears to decrease the risk of microvascular renal progression, but whether this effect is from the medication or tighter glucose control is unclear, as the original trial did show a statistically lower HbA1C in the empagliflozin group.

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Does this nasal steroid cause birth defects? May not pass the sniff test

Bérard A, Sheehy O, Kurzinger ML, Juhaeri J. Intranasal triamcinolone use during pregnancy and the risk of adverse pregnancy outcomes. *J Allergy Clin Immunol*. 2016; 138(1):97–104.e7.

This Canadian population-based cohort study examined the effect of intranasal triamcinolone on birth defects, spontaneous abortions, and small-for-gestational age (SGA) compared with other intranasal steroids or no exposure.

The national Public Prescription Drug Insurance database was examined for dispensed prescriptions to pregnant patients and the Quebec Pregnancy Cohort database was examined for the diagnosis of major congenital malformations, SGA, and cases of spontaneous abortions. More than 140,000 patients were included in the congenital malformation analysis (0.2% were exposed to intranasal triamcinolone) and more than 150,000 patients were included in the SGA analysis (0.3% were exposed to intranasal triamcinolone). Multiple confounders were considered to include sociodemographic factors; maternal age; and chronic conditions such as hypertension, diabetes, and chronic rhinitis.

Compared with no exposure, intranasal triamcinolone was associated with no increased risk for overall major congenital malformations, SGA, or spontaneous abortion. However, compared with no exposure, risk of respiratory malformations (larynx, trachea, bronchus, and choanal atresia) was higher in the triamcinolone group (5 vs 632 patients; adjusted odds ratio [OR] 2.7; 95% CI, 1.1–6.6) but not in the other intranasal steroid group (adjusted OR 0.85; 95% CI, 0.47–1.6).

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

Bottom line: This study found an increased risk of respiratory malformations with triamcinolone use, but causality is uncertain. Very few respiratory malformations cases were noted overall and, without a sensitivity analysis, it is unclear how robust these findings are. Unmeasured confounders also remain a concern. EBP

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