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EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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FPIN
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.

TABLE OF CONTENTS

VOL 26 | NO. 3 | March 2023

EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

EDITORIAL

DIVING FOR PURLs

IN DEPTH

GEMS

HELPDESK ANSWERS

SPOTLIGHT ON PHARMACY

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

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.

EDITORIAL POLICY

Statements and opinions expressed in articles and communications in this journal are those of the author(s) and not necessarily those of the editor, publisher, or any organizations endorsing this journal. The Publisher and editors of EBP do not endorse any methods, products, or ideas mentioned in the journal, and disclaim any liability which may arise from any material herein. Unless noted, authors have reported no competing interests and have nothing to disclose.

DISCLOSURE

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Scottish Sage

When I was in medical school and residency, people were always trying to give me advice. A lot it was rather dubious. Some terrible examples included:

"Trust no one."

"Present like you have no doubts."

"There are only two acceptable excuses to call in sick: if you're taking triple antibiotics or have blasts on a peripheral smear."

But not all advice was patently awful. One of the most curious, and linguistically compelling, tidbits came from an attending from Scotland who told me in his thick highland accent, "*Laddie, ne'er use a droog that's oonder 10 yehrs auld. They're noo safe and ye canna tell whot troobles will be a'cummin' doon the rood*. *Best ta use gener'rick*."

Translated, my attending was warning me not to be dazzled by newly released medications. He explained that, in his experience, unexpected toxicities were frequently uncovered in post-marketing surveillance and he did not want to put his patients at risk.

Was he right about that?

In 2017 a research team reviewed safety information on 222 novel therapeutic agents approved by the Food and Drug Administration (FDA) for use in the US between 2001 and 2010 and followed them for a mean of 11 years. They tallied up all post-release safety interventions by the FDA. A sobering 32% of new medications had some safety action after release. Three were withdrawn (valdecoxib, tegaserod, and efalizumab), 43 agents received new or additional black box warnings, and the FDA issued safety bulletins for 44. The median time from approval to a safety intervention was 4.2 years. Curiously, agents for psychiatric diseases garnered the most safety actions and hematology/onclology medications garnered the fewest (60% vs 21%; $P=.006$). Risk also appeared higher with novel biologics and medications receiving accelerated FDA approval.[1]

So, my attending was correct after all: drugs commonly reach the marketplace years before all the important toxicities are identified. Now I can confidently give the same advice that I once skeptically received: not only are generic medications less expensive, they are also a safer way of helping our patients make it "*doon the rood*."

Jon O. Neher

DOI 10.1097/EBP.0000000000001875

Reference

1. Downing NS, Shah ND, Aminawung JA, et al. Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *JAMA*. 2017; 317(18):1854–1863.

The value of a good breakfast

King DE, Xiang J. A Relationship Between Mortality and Eating Breakfast and Fiber. J Am Board Fam Med. 2021; 34(4):678-687. doi:10.3122/jabfm.2021.04.210044

DOI 10.1097/EBP.0000000000001647

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	No

This is a post-hoc, retrospective cohort analysis (n=5,761) of information previously published in the National Health and Nutrition Examination Survey (NHANES) database for 1999–2002. The primary outcomes were all-cause mortality and mortality related to cardiovascular disease (CVD) in subjects who ate breakfast compared with those who did not. The secondary outcome was any difference in all-cause mortality in subjects who ate a high-fiber breakfast versus those who ate a low-fiber breakfast. The tertiary outcome was any difference in all-cause mortality between those who ate fiber with breakfast and those who ate fiber with meals other than breakfast. Data extraction was by chart review methodology. A statistically significant difference was found in many demographic categories between groups, including age, sex, race, body mass index, level of education, daily calorie intake, and daily fiber intake. Statistically significant differences were also observed between groups in the prevalence of hypertension, diabetes mellitus (type not specified), and CVD. Eating breakfast was associated with reduced all-cause mortality by 31% (hazard ratio [HR] 0.69; 95% CI, 0.57–0.84) and cardiovascular mortality by 55% (HR 0.45; 95% CI, 0.32–0.63). Eating a high-fiber breakfast was associated with a 27% reduction in all-cause mortality (HR 0.73; 95% CI, 0.61–0.88). Eating fiber at times other than breakfast showed no mortality benefit. Because of the many demographic differences between the groups, the results are subject to significant confounding.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching Up-to-date, DynaMed, USPSTF, and PubMed with the terms "breakfast," "fiber," and "mortality" to find additional literature to place this research into the context of current clinical practice.

Bottom line: This study demonstrates an association between eating any breakfast, especially a high-fiber breakfast, and reduced mortality. It provides support for the common practice of counseling patients that breakfast is one of the most important meals of the day. No association was found between a high-fiber diet at other times of the day and a mortality benefit, likely because of uncorrected confounding between group demographics and eating patterns.

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Hospital-at-home care as an alternative to inpatient admission for patients with chronic disease

Arsenault-Lapierre G, Henein M, Gaid D, Le Berre M, Gore G, Vedel I. Hospital-at-Home Interventions Versus In-Hospital Stay for Patients With Chronic Disease Who Present to the Emergency Department: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021;4(6): e2111568. Published 2021 Jun 1. doi:10.1001/jamanetworkopen.2021.11568

DOI 10.1097/EBP.0000000000001627

This systematic review and meta-analysis compared hospital-at-home (HaH) care as a substitute for standard in-hospital care for patients with a chronic disease presenting for care to the emergency department. Investigators performed the review using four online databases guided by the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines. Selected studies were randomized clinical trials that used at least one patient-oriented outcome and assessed

patients with at least one chronic condition who presented for acute care to an emergency department. Patients were randomized to receive HaH care as a substitute for standard inpatient admission. HaH care was defined as at least one home visit from a nurse or physician who provided treatment that would have otherwise been given in the hospital (most commonly monitoring, face-face clinical care, diagnostic testing and other treatment, such as intravenous medications). Nine studies (N=959) from four different countries met inclusion criteria, with a median patient age of 71 years old. The HaH and in-hospital groups had similar characteristics, but included fewer women in the in-hospital group (40.4% vs 31.2%). Most of the patients had either congestive heart failure (CHF) or COPD. Outcomes analyzed by meta-analysis included mortality, readmission, length of treatment, and long-term care admission. The median follow-up period was three months and ranged from 1 to 12 months. Mortality rates did not differ between the HaH and in-hospital groups (relative risk [RR] 0.84; 95% CI, 0.61–1.15), but lower rates of readmission were noted in the HaH group (RR 0.74; 95% CI, 0.57–0.95). Length of treatment was longer in the HaH group (mean difference=5.4 days; 95% CI, 1.9–9.0 days). Risk of long-term care admission was lower in the HaH group (RR 0.16; 95% CI, 0.03–0.74). Limitations included a large heterogeneity, a scarcity of details about medical interventions provided in HaH studies, predominate analysis of only two chronic diseases (CHF and COPD), and underrepresentation of female patients.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching [UpToDate] with the terms [hospital-at-home, alternatives to hospital care] to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	No
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: HaH treatment may be a safe alternative to hospitalization for patients with a chronic medical condition (especially CHF and COPD) who present to the emergency department for treatment. This systematic review and meta-analysis demonstrated lower rates of readmission and admission to long-term care facilities in HaH groups compared with traditional in-hospital care, and no difference in mortality. Currently, this intervention is not easily implementable by most family physicians outside of the few large hospital systems in the United States that have an established HaH care infrastructure.

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Individualizing diabetes care without sacrificing A1c reduction

Giugliano D, Longo M, Caruso P, et al. Feasibility of Simplification From a Basal-Bolus Insulin Regimen to a Fixed-Ratio Formulation of Basal Insulin Plus a GLP-1RA or to Basal Insulin Plus an SGLT2 Inhibitor: BEYOND, a Randomized, Pragmatic Trial. Diabetes Care. 2021;44(6): 1353-1360. doi:10.2337/dc20-2623

DOI 10.1097/EBP.0000000000001650

This noninferior, randomized, open-label, parallel-group, active-control, single-center trial evaluated the efficacy and safety of switching patients from basal-bolus insulin (BBI) regimens to either basal insulin plus GLP1A in a fixed dose (B-GLP1A) or basal insulin plus SGLT2-I (B-SGLT2i) for patients with established type 2 diabetes. To be included, patients needed to be seen by an endocrinology division in Italy, be at least 35 years old, have an A1c of at least 7.5%, and be on current four injections of insulin daily. Patients were excluded if they had a history of pancreatitis or pancreatectomy, previous use of GLP1A or SGLT2i, impaired kidney function, or history of cancer within the past five years. Patients in the BBI group continued their four doses of insulin and were instructed to self-adjust the insulin based on blood

glucose monitoring throughout the day. Patients in the B-GLP1A group discontinued the previous insulin regimen and started a fixed dose, daily injection at recommended doses. Patients in the B-SGLT2i group continued their previous basal insulin only and started one of three SGLT2is are recommended doses. Both intervention groups were instructed to adjust basal insulin dose based on morning fasting readings. The primary outcome of this trial was noninferior change in HbA1c at six months (meaningful difference margin was set at 0.3%). Secondary outcomes included proportion of participants reaching certain A1c goals, hypoglycemia, total insulin doses, and patient satisfaction.

A total of 101 patients were in the BBI group, 102 in the B-GLP1A group, and 102 in the B-SGLT2i group. Patients were 61 years old on average, had diabetes for 17 years on average, and weighed 87 kg on average. Entering HbA1cs were 8.5% on average, and total insulin doses were approximately 50 units a day. The primary end point met noninferiority with resulting HbA1cs of –0.6%, –0.6%, and –0.7%, respectively ($P=.356$). Proportions of patients achieving an HbA1c <7%, 7.5%, and 8% were not different between groups. As expected, insulin doses were highest in the BBI group at the end of the study with an average of 62 units, whereas inulin doses in B-GLP1A were 27 units and in B-SGLT2i were 21 units per day. Hypoglycemia (<70 mg/dL with signs or symptoms) occurred in 17.8% of BBI patients, 7.8% B-GLP1A patients, and 5.9% B-SGLT2i patients. No patients dropped out of the BBI group, whereas 12 and 9 patients dropped out of the B-GLP1A and B-SGLT2i groups, respectively. Most commonly, patients dropped out for failing to maintain the HbA1c level below baseline. Satisfaction scores increased in both intervention groups and remained the same in the BBI group.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here.

Does this meet PURL criteria?			
Relevant	No	Medical care setting	Yes
Valid	No	Implementable	Yes
Change in practice	Yes	Clinically meaningful	No

Bottom Line: Although this study looks like a practice changer on the surface, identifying and applying the findings to patients in practice will be difficult. When providing patient-centered care, providers are likely to introduce GLP1A or SGLT2i without replacing meal-time bolus insulin, especially if patients are not at HbA1c goals. Being an open-label and single-center trial challenges external validity.

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The author declares no conflicts of interest.

Empagliflozin reduces heart failure hospitalizations in patients with HFpEF

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021; 385(16):1451-1461. doi:10.1056/NEJMoa2107038

DOI 10.1097/EBP.0000000000001679

This double-blind, parallel-group, event-driven trial randomized 5,988 adult patients (1:1 ratio) with chronic heart failure and a left ventricular ejection fraction of >40% to either placebo or empagliflozin, 10 mg per day. Patients were required to have a pro-B-type natriuretic peptide level >300 pg/mL (>900 pg/mL with an atrial fibrillation history) and NYHA II-IV symptoms at baseline. The primary outcome was a composite of cardiovascular death or first hospitalization for heart failure, and the secondary outcomes were all hospitalizations for heart failure and the rate of decline in eGFR. Groups were similar at baseline and followed for a median of 26.2 months. A primary outcome event occurred in 415 patients (13.8%) in the empagliflozin group and in 511 patients (17.1%) in the placebo group (hazard ratio [HR] 0.79; 95% CI, 0.69–0.90; $P<.001$). Specifically, hospitalization for heart failure occurred in 259 patients (8.6%) with empagliflozin versus 352 patients (11.8%) with placebo (HR 0.71; 95% CI, 0.60–0.83), and cardiovascular death occurred in 219 patients (7.3%) with empagliflozin versus 244 patients (8.2%) with placebo (HR 0.91; 95% CI, 0.76–1.09). The total number of hospitalizations for heart failure was 407 with empagliflozin versus 541 with

placebo (HR 0.73; 95% CI, 0.61–0.88; $P<.001$), and the rate of decline in the eGFR was –1.25 to –2.62 mL/min/1.73 m^2 per year ($P<.001$) in the empagliflozin group compared with placebo group, meaning those on empagliflozin had preserved renal function compared with those taking placebo. A total of 422 patients (14.1%) in the empagliflozin group and 427 patients (14.3%) in the placebo group died from any cause (HR 1.00; 95% CI, 0.87–1.15). Genital infections (2.2% vs 0.7%) and urinary tract infections (9.9% vs 8.1%) were more common in the empagliflozin group.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. An additional literature search was conducted by searching Essential Evidence Plus with the terms Heart Failure with Preserved Ejection Fraction to find additional literature to place this research into the context of current clinical practice.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: Empagliflozin reduces hospitalization for heart failure, regardless of the presence or absence of diabetes but does not seem to affect cardiovascular or all-cause mortality.

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The authors declare no conflicts of interest.

Does exercise delay the need for total knee arthroplasty in adults with osteoarthritis?

EVIDENCE-BASED ANSWER

About a third of patients initially willing to undergo total knee arthroplasty (TKA) are willing to forgo TKA after 12 months of an individualized exercise therapy plan. Patients with walking difficulties are more likely to still want TKA at 12 months (SOR: **B**, prospective cohort study). Exercise therapy improves quality of life and pain scores, with a peak at 2 months and gradual decline to baseline levels by 9 to 18 months (SOR: **A**, systematic review/meta-analysis).

DOI 10.1097/EBP.0000000000001808

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 Swedish observational study assessed the willingness of patients with knee osteoarthritis (OA) to reconsider total knee arthroplasty (TKA) 3 and 12 months after first-line education and a personalized exercise program.[1] Patients had clinical or radiographic knee or hip OA (total N=30,578; knee OA: N=20,649). All patient received at least two sessions of education on the pathology and management options of OA, followed by a personalized exercise program to be performed over a 6-week period. The primary outcome measured was willingness to undergo TKA at baseline and both follow-ups. Variables assessed included age, body mass index (BMI), pain intensity, pain self-efficacy, presence of walking difficulty, and quality of life (QoL). Among patients initially willing to undergo TKA (N=4,916), 35% no longer considered surgery at 12 months (N=1,710). Patients initially willing to undergo TKA were overall younger, female, with a higher BMI, baseline pain, lower pain self-efficacy, and lower QoL. Patients with walking difficulties were more likely to be willing to undergo TKA at 3 and 12 months (odds ratio [OR] 3.46; 95% confidence interval [CI], 2.85–4.20 and odds ratio [OR] 3.55; 95% CI, 2.83–4.47, respectively). This study was limited by difficulty monitoring adherence and frequency of the exercise program and baseline cultural differences in European and North American outlooks on walking and physical activity.

A 2019 systematic review and meta-analysis of 77 RCTs (N=6,472) evaluated the efficacy of exercise therapy on pain, function, performance, and QoL in patients with knee and hip OA.[2] Patients had knee or hip OA, had not undergone joint replacement surgery, and were stratified by age (<60 or ≥60 years), BMI (<30 or ≥30 kg/m^2), and percentage of female participants (<60%, 60%–80%, and ≥80%). Exercise-only interventions (regardless of type) were compared with usual care (no intervention, usual physician follow-up, or "wait list" for intervention after study). The primary outcome measured was pain level, with self-reported function, objective performance, and QoL as secondary outcomes. Different studies in the meta-analysis had different pain scales and objective performance definitions (walking distance/time were given priority because they were relatively standard among trials, followed by joint specific parameters [strength, power, and range of motion] if no gait parameters were available). The meta-analysis made no comment on specific parameters for measuring QoL or self-reported function improvement because they varied in the studies. The reports were grouped into time-based intervals, with the primary time point set to 8 weeks. The outcomes were calculated as an effect size (ES; using between-group standardized mean difference following Cohen's method) with 0.2, 0.5, and 0.8 indicating small, medium, and large effect, respectively. At 8 weeks, exercise had a moderate benefit on pain relief (ES 0.56; 95% CI, 0.44–0.57), function (ES 0.50; 95% CI, 0.38–0.63), and performance (ES 0.46; 95% CI, 0.35–0.57). It also had a mild benefit on QoL (ES 0.21; 95% CI, 0.11–0.31). The benefits of exercise therapy on reported outcomes peaked 2 months after initiation, gradually fell over time, and became no better than usual care at 9 to 18 months. Patients <60 years old (12 RCTs, N=591; ES 1.32; 95% CI, 0.79–1.86), with knee OA (55 RCTs, N=3,750; ES 0.64; 95% CI, 0.51–0.78), who are not awaiting joint replacement (55 RCTs, N=4,481; ES 0.62; 95% CI, 0.49–0.75) had the greatest pain relief with exercise therapy. Conversely, patients awaiting TKA (14 RCTs, N=791; ES 0.33; 95% CI, 0.04–0.63) had only mild benefit in pain relief. Some

limitations of this study included the varied outcomes measured, missing data on important covariates, incomplete reports of outcomes, varied outlines of exercise therapy, and an inconsistent definition of "usual care" for OA. EBP

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Molnupiravir: an outpatient treatment option for symptomatic COVID-19 in unvaccinated adults

Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalized Patients

Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et. al. Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalized Patients. *N Engl J Med*. 2022;386(6): 509-520. DOI 10.1097/EBP.0000000000001737

KEY TAKEAWAY: Molnupiravir reduces the risk of hospitalization or death in unvaccinated adults with COVID-19.
STUDY DESIGN: Phase III, double-blind, randomized, placebo-controlled trial.
LEVEL OF EVIDENCE: Step 2.

BRIEF BACKGROUND INFO: There have been almost 270 million cases and over 5.2 million COVID-19–related deaths worldwide. It has placed a burden on healthcare systems all over the world, with no outpatient treatments available other than symptom management. New medications are needed for management of COVID-19.

PATIENTS: Nonhospitalized, unvaccinated adults with laboratory-confirmed COVID-19.
INTERVENTION: 800 mg molnupiravir twice daily for five days.
CONTROL: Placebo twice daily for five days.
OUTCOME: Hospitalization, death.

Secondary Outcomes: symptoms, adverse events.
METHODS BRIEF DESCRIPTION:

- Patients were unvaccinated adults with mild to moderate COVID-19, at least one risk factor for severe COVID-19, and symptoms starting within the past five days.
- Each patient was randomly assigned to receive molnupiravir or placebo twice daily for five days.
- Patients reported their symptoms daily in paper diaries from initial date of randomization through day 29.
- Information regarding hospitalization status, viral load, and symptom improvement and progression were collected on days 1, 3, 5, 10, 15, and 29.
- Information regarding adverse events related to the treatment was collected during the trial period and for 14 days after.

INTERVENTION (# IN THE GROUP): 716
COMPARISON (# IN THE GROUP): 717

FOLLOW-UP PERIOD: 29 days

RESULTS:
Primary outcome
- Molnupiravir decreased the risk of hospitalization or death compared with placebo (7.3% vs 14.1%, respectively, a treatment difference of –6.8%; 95% CI, –11.3 to –2.4; P=.001).

Secondary outcomes
- More patients in the molnupiravir group reported symptomatic improvement or resolution; however, this was not statistically significant.
- Both groups had similar rates of at least one adverse event.
- Diarrhea, nausea, and dizziness were the most common adverse events related to molnupiravir.

LIMITATIONS: Funded by the manufacturer of molnupiravir. EBP

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The author declares no conflicts of interest.
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 U.S. Navy Medical Department, the Navy at large, or the Department of Defense.
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Does vitamin B_{12} supplementation in elderly patients with low or normal vitamin B_{12} levels improve cognition?

EVIDENCE-BASED ANSWER

No. Elderly patients with or without cognitive impairment in the form of Alzheimer disease or dementia do not show an increase in their cognitive function after supplementation with vitamin B_{12} (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Elderly patients with marginal vitamin B_{12} levels do not show neurological improvement in response to vitamin B_{12} supplementation in comparison with patients with higher baseline vitamin B_{12} levels (SOR: **C**, secondary analysis of RCTs).

DOI 10.1097/EBP.0000000000001816

This clinical quest was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 meta-analysis of four randomized controlled trials (RCTs; N=679) examined the effectiveness of supplementing folic acid and vitamin B_{12} versus placebo on cognition and homocysteine levels in elderly patients with Alzheimer disease or dementia.[1] Patients were of an average age of 77 years old with a confirmed diagnosis of Alzheimer disease or dementia. Individuals were given B vitamins, folic acid, vitamin B_{12}, multivitamins, or combinations of these supplements for between 6 and 18 months and all were compared with placebo groups (dosing not available). Cognition was measured using the mini-mental status examination (MMSE) and Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog). The MMSE is a validated tool measuring cognition performance with a maximum score of 30, and a score of <24 is indicative of cognitive impairment. After pooling data from all four trials, supplementation with B_{12} did significantly reduce homocysteine levels compared with the placebo (mean difference [MD] –3.6 picomol/mL; 95% CI, –5.6 to –1.6). Despite this, no significant difference in MMSE scores occurred between intervention and control groups (MD 0.03; 95% CI, –0.52 to 0.57). Limitations include a difference in therapy time, short duration time, and small sample size.

A 2017 secondary analysis of a double-blinded RCT (n=201) investigated the effects of vitamin B_{12} supplementation on neurological outcomes.[2] Patients were recruited from seven general practices in Southeast England aged 75 years old or older with marginal vitamin B_{12} levels (serum vitamin B_{12} concentrations >106 and <210 picomol/L) and who did not have anemia (hemoglobin >109 g/L for women and >119 g/L for men). Individuals with significant cognitive impairment, diabetes, and or those in nursing homes were excluded. The treatment group was given 1 mg of vitamin B_{12} daily for 12 months (n=99) and the others were given placebo (n=109). Linear regression models were used to determine associations between change in vitamin B_{12} status and neurologic response to vitamin B_{12} supplementation. No change was found in neurological responses to changes in vitamin B_{12} levels from supplementation. Limitations of this study were small sample size and the short duration of the study. EBP

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Are benzodiazepines harmful in the treatment of acute delirium?

EVIDENCE-BASED ANSWER

In the intensive care unit (ICU), benzodiazepine use likely increases the risk of delirium, though the magnitude of this effect is uncertain (SOR: **B**, systematic review of heterogeneous randomized controlled trials [RCTs] and cohort studies). In non-ICU settings, benzodiazepine treatment of delirium may be roughly comparable with haloperidol and chlorpromazine treatment for nonwithdrawal delirium, although data are minimal (SOR: **C**, 2 small RCTs).

DOI 10.1097/EBP.0000000000001764

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2018 systematic review of 49 studies (10 randomized controlled trials [RCTs], 38 cohort studies, 1 point-prevalence study; N=11,138) examined the association between benzodiazepine use in the intensive care unit (ICU) and neuropsychiatric complications.[1] The studies included adult patients admitted to the ICU for any reason. All studies evaluated benzodiazepine treatment as the intervention or exposure, without stipulation or comment on the specific type, indication, or dosage. The review notes two trials specifically compared benzodiazepine treatment to propofol and dexmedetomidine, but otherwise does not comment on comparator groups used. Although the review included studies that reported on a variety of neuropsychiatric outcomes, the new diagnosis of delirium was the primary outcome in 35 studies. The Confusion Assessment Method was the most frequently used standardized assessment to diagnose delirium, usually measured daily during hospitalization. Overall, 10 of 13 studies deemed to be of high methodological quality found benzodiazepine use to be associated with an increased risk of developing delirium. Furthermore, high daily dose, continuous administration, and specific drugs (midazolam and lorazepam) were associated with the highest risk of delirium. Limitations included heterogeneity in study design, indication for treatment, and dose and type of benzodiazepine, limiting generalizability. Furthermore, the review only commented on the number of studies showing an association and did no pool or comment on specific data, preventing quantification of the effect.

A 2020 meta-analysis of two RCTs (N=88) examined the effects and safety of benzodiazepine treatment of patients with delirium in non-ICU settings.[2] The review included adult patients in long-term care nursing facilities and non-ICU hospital facilities with delirium, diagnosed using Diagnostic and Statistical Manual criteria or the Delirium Rating Scale. The studies excluded patients with alcohol or benzodiazepine withdrawal-related delirium. Studied benzodiazepines could be any type or dose. Comparisons included placebo and other nonbenzodiazepine treatments of delirium. The primary outcome was change in delirium severity as assessed by the Memorial Delirium Assessment Scale (30-point scale with higher scores indicating increased delirium severity) measured at baseline, two, four, and eight hours. Secondary outcomes included length of hospital stay, all-cause mortality, and adverse medical events measured by the Extrapyramidal Symptom Rating Scale. One RCT (n=58) comparing treatment with benzodiazepines and haloperidol versus placebo and haloperidol found no difference in delirium severity (mean difference [MD] 2.1; 95% CI, –1.0 to 5.2), hospital length of stay (MD 0.0; 95% CI, –3.5 to 3.5), or all-cause mortality (risk ratio [RR] 0.31; 95% CI, 0.04–3.0). The other RCT (n=30) compared treatment with benzodiazepines versus chlorpromazine and found no difference in delirium severity (MD 5.2; 95% CI, –0.33 to 11), adverse events (MD 7.1; 95% CI, –0.42 to 15), or all-cause mortality (RR 0.91; 95% CI, 0.22–3.3). The same study compared benzodiazepines with haloperidol and also found no differences in delirium severity (MD 5.4; 95% CI, –0.01 to 11), adverse events (MD 6.7; 95% CI, –1.5 to 15), or all-cause mortality (RR 1.8; 95% CI, 0.34–9.9). Limitations included low number of available studies and low sample sizes, limiting power and confidence in the results. EBP

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Which anti-nausea medications are more likely to increase QTc interval?

EVIDENCE-BASED ANSWER

Ondansetron, haloperidol, and aprepitant have little effect on the QTc interval, whereas droperidol prolongs QTc compared with placebo (SOR: **B**, meta-analysis of low-quality studies). Dolasetron combined with dexamethasone significantly increases risk of QTc prolongation compared to ondansetron combined with dexamethasone (SOR: **B**, systemic review). A single dose of ondansetron 8 mg is associated with transient QTc prolongation when compared to 4 mg (SOR: **B**, single randomized controlled trial).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

In 2020, a network meta-analysis of 585 randomized controlled trials (RCTs; N=97,516) compared both efficacy and safety of different antiemetics for preventing postoperative nausea and vomiting.[1] RCTs were selected that compared one or more antiemetics from six classes (5-HT_3 receptor antagonists, D2 receptor antagonists, NK1 receptor antagonists, corticosteroids, antihistamines, and anticholinergics) in adults >18 years old (mean 42 years old, 83% women) undergoing any type of surgery with general anesthesia. In some studies, those with postoperative nausea and vomiting and motion sickness were excluded. The primary outcomes were vomiting and serious adverse events, and secondary outcomes included various specific side effects such as QTc prolongation, which was assessed by 18 of the RCTs (N=4,440). Assessment of 5-HT_3 receptor antagonists showed that ondansetron had little to no effect on QTc prolongation compared with placebo (relative risk [RR] 0.93; 95% CI, 0.18–4.76). Among D2 receptor antagonists, droperidol increased QTc prolongation (RR 1.3; 95% CI, 0.71–2.3), and haloperidol had little to no effect on QTc prolongation (RR 0.98; 95% CI, 0.20–4.9), both with low certainty of evidence. Assessment of NK1 receptor antagonists showed that aprepitant may have little to no effect on QTc prolongation (RR 0.96; 95% CI, 0.19–4.9), with very low certainty of evidence. Assessment of corticosteroids showed that reduction of QTc prolongation by dexamethasone (RR 0.75; 95% CI, 0.05–12) remains uncertain, with very low certainty of evidence. Limitations include low certainty of evidence because of small sample size for single drugs compared with placebo, lack of reporting relevant safely outcomes in 44% of studies, risk of bias of selective outcomes reporting of side effects, and lack of detailed definition of QTc prolongation.

In 2016, a systemic review and network meta-analysis of four RCTs (N=3,358) compared the safety and effectiveness of serotonin receptor antagonists on QTc prolongation.[2] The trials included elderly, adult, and pediatric patients undergoing various chemotherapy regimens. The medications varied but included 5-HT_3 antagonists (dolasetron, ondansetron, palonosetron, and granisetron) alone or combined with dexamethasone for a total of seven treatments. Although pairwise meta-analysis was not possible as the RCTs did not evaluate the same intervention, the analysis noted that patients taking ondansetron with dexamethasone had lower odds of QTc prolongation compared with dolasetron and dexamethasone (odds ratio 0.34; 95% CI, 0.24–0.47). None of the other five comparisons revealed a significant difference.

A 2014 single-center RCT (n=129) compared effects of prophylactic ramosetron and ondansetron on QTc interval.[3] Patients were adults (20–75 years old) undergoing elective laparoscopic cholecystectomy in Seoul, South Korea. Patients were split into three groups to receive IV ondansetron 4 mg, ramosetron 0.3 mg, or ondansetron 8 mg. All medications were given about 15 minutes before the end of surgery. The QT interval was measured immediately before injection and then once every minute for 10 minutes after administration. The QTc was considered prolonged if >460 ms. The QTc interval was longer at one, two, three, four, and five minutes compared with ondansetron 4 mg group ($P<.05$). The QTc interval was not changed in both ondansetron 4 mg and ramosetron 0.3 mg treatment groups. Limitations include the use of the ondansetron 4

mg group as the control group, and the patients' QTc were only monitored for a short window of 10 minutes. EBP

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Is conservative therapy or platelet-rich plasma therapy more effective for the treatment of Achilles tendinosis?

EVIDENCE-BASED ANSWER

In the treatment of Achilles tendinosis, platelet-rich plasma (PRP) injections are no better than saline injections when added to eccentric exercise (SOR: **A**, meta-analysis). Patients who fail eccentric exercises may benefit from PRP injections (SOR: **C**, case series).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

In a 2018 meta-analysis, four randomized controlled trials (RCTs; N=170) compared the effectiveness of platelet-rich plasma (PRP) injection plus eccentric strength training with placebo injection plus eccentric strength training for the management of Achilles tendinopathy.[1] Trials needed to be RCTs, enroll adult patients with Achilles tendinopathy, and compare PRP injection with saline injection. Victorian Institute of Sport Assessment-Achilles (VISA-A) scores, tendon thickness change, color Doppler activity, and other functional outcomes were used. Trials that included patients who received glucocorticoid injection within the last 6 months, Achilles tendon rupture or tear, previous Achilles tendon surgery, and known inflammatory diseases were excluded. Patients in the PRP injection group received no standardized injection technique; however, all patients followed the same rehabilitation and eccentric program, which consisted of one week of less than 30-minute walking daily and then one week of stretching only with walking, followed by 12 weeks of eccentric exercises daily. The primary endpoint used was improvement in the VISA-A score, which is a validated questionnaire that ranges from 0 to 100 points, with higher scores representing increased activity and less pain. The minimum clinically important difference of the VISA-A score was 12. Secondary outcomes were tendon thickness and color Doppler activity. Follow-up times ranged from 3 to 12 months No difference was noted between the PRP and saline injection groups regarding the primary outcome of measured VISA-A scores (4 studies, N=170; mean difference = 5.3; 95% CI, –0.7 to 11.3; P=.085). No difference was noted between the PRP and saline groups regarding the secondary outcomes of the study, including tendon thickness change and color Doppler activity. The included trials listed no harms of the interventions. This meta-analysis was noted to have several limitations, foremost in regards to the population of the trials that drew from the general population and had few elite athletes with far fewer women than men.

A case series examined the effectiveness of noninsertional Achilles tendinopathy treatment with autologous PRP.[2] Fifteen Achilles tendons of 14 randomly chosen patients with an average age of 40 years old presented to the clinic seeking treatment for symptoms of noninsertional tendinopathy. Patients with symptomatic insertional tendinopathy were excluded. All patients had failed various conservative treatment

modalities, including eccentric exercise, with an average treatment duration of seven months. All patients had at least a three-month interval since previous treatments. All patients received an ultrasound (US)-guided injection with an average of 3 mL PRP into the hypoechogenic areas of the affected tendons and underwent the same remobilization protocol. The primary outcome was improvement of symptoms of noninsertional Achilles tendinopathy using the American Orthopedic Foot and Ankle Society scale for the hind foot and the VISA-A scale. Scores of both scales range from 0 to 100, with higher scores reflecting less symptoms and improvement in function. The secondary outcome of the study was Achilles tendon thickness and vascular flow intensity using Power-Doppler ultrasonography. Primary and secondary outcomes were measured at 6 weeks and 3, 6, and 18 months. Injection of autologous PRP was associated with increases in both scales (over baseline) at 6 weeks and 3, 6, and 18 months. On US, all tendons were thinner and vascular intensity within tendons was increased at 6 weeks and 3 months and were found to be absent at 18 months. No documented harms of the intervention were included in the study. EBP

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What duration of permissive hypertension leads to best outcomes after an ischemic stroke?

EVIDENCE-BASED ANSWER

After an acute ischemic stroke (AIS), time to initiation of BP treatment does not affect the rate of death or disability (SOR: **A**, systematic review of randomized control trials). When comparing 24 h off all hypertensive medications with early initiation of antihypertensive medications in patients with AIS, no difference is observed in the risk of death or major disability (SOR: **B**, single large randomized control trial). The American Heart Association and American Stroke Association generally recommend permissive hypertension with a blood pressure goal of ≤220/120 mmHg for the first 48 to 72 h in patients with AIS (SOR: **C**, expert consensus).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2014 systematic review of 24 randomized control trials (RCTs; N=15,432) assessed whether initiation time of blood pressure (BP)–lowering treatment after an acute stroke affects death or disability.[1] Included patients were at least 18 years old and diagnosed with an acute ischemic or hemorrhagic stroke. Patients assigned to the treatment group received a variety of antihypertensive medications, including alpha-2 adrenergic agonists, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, calcium channel blockers, nitric oxide donors, and thiazide-like diuretics. Trials varied in time to treatment initiation with some as early as 6 h after recruitment. BP targets were not defined. Control groups

received placebo. The primary outcome was death and disability by the end of the trial (>1 month after stroke). Disability was defined as a modified Rankin score > 2 (range 0–6, with 0 indicating no symptoms and 6 indicating death). In the trials only including patients with acute ischemic stroke (AIS), time to BP treatment did not have a significant effect on death or disability by trial end (8 RCTs, N=11,015; odds ratio [OR] 1.0; 95% confidence interval [CI], 0.92–1.1). Limitations included variability in the method of obtaining and recording BP across the multiple trials. In addition, the included populations tended to be younger and have fewer comorbidities which could affect generalizability.

A 2014 multicenter RCT (n=4,071) assessed the effect of treating hypertension within the first 24 h after AIS.[2] Included patients were at least 22 years old with an AIS diagnosed using neuroimaging and systolic BP (SBP) between 140 and 220 mmHg. Researchers excluded patients warranting thrombolysis or those with SBP >220 mmHg, severe cardiac or vascular disease, and coma. The intervention group received active BP management, with a goal of 10% to 25% reduction of SBP within the first 24 h of AIS diagnosis and a BP of <140/90 mmHg within seven days. The treatment group received various antihypertensive agents (including angiotensin-converting enzyme inhibitors, calcium channel blockers, and thiazide-like diuretics), either individually or in combination, to achieve BP targets. Researchers stopped all antihypertensive medications during hospitalization in the comparator group. After hospital discharge, patients in both groups were prescribed antihypertensive medications. The primary outcome was a combination of death and major disability (defined as a modified Rankin score of 3–5) at 14 days post-AIS diagnosis or hospital discharge (if <14 days). Secondary outcomes included a combination of all-cause mortality and major disability at 3 months post-diagnosis. At 14 days or hospital discharge, the composite outcome of death and major disability was not significantly different between the treatment and control groups (OR 1.0; 95% CI, 0.88–1.1). On subgroup analysis, those in the treatment group who received antihypertensive treatments at 24 h or greater after stroke onset did have a reduced odds of the primary outcome (OR 0.73; 95% CI, 0.55–0.97). At 3 months post-treatment, the number of patients who experienced death or major disability was not different between the two groups (OR 0.73; 95% CI, 0.89–1.3). This study was limited by antihypertensive treatments not being standardized and a strictly Chinese study population that may limit generalizability.

The 2019 consensus and evidence-based practice guidelines from the American Heart Association and the American Stroke Association updated the 2018 guidelines in the early management of patients with AIS.[3] The American Heart Association/American Stroke Association guidelines recommended that patients with BP <200/120 mmHg are able to initiate or reinitiate treatment of hypertension within the first 48 to 72 h after an AIS if they did not receive intravenous alteplase or thrombectomy. The guideline authors note that starting treatment seems to be safe but not associated with improved mortality or functional outcomes. This recommendation was based on the review of high-quality evidence, including the above studies. EBP

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Is a five-tier classification of fetal heart tracing preferable to a three-tier system?

EVIDENCE-BASED ANSWER

A five-tier classification system for fetal heart tracings is preferable to a three-tier-system. A five-tier system may more accurately identify tracings of infants with acidemia than a three-tier system (SOR: **C**, small case-control studies). A five-tier system may also have better interobserver agreement when identifying tracings of infants with acidemia (SOR: **C**, case-control study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 retrospective case-control study (n=715) compared the federation of gynecology and obstetrics (FIGO) three-tier, National Institute of Child Health and Human Development (NICHD) three-tier, and Parer and Ikeda five-tier FHT systems' ability to identify risk for fetal asphyxia in combination with maternal risk factors.[1] Patients were term parturients delivering at a hospital in Thailand. The average patient age was 29 years old; no further demographics were reported. The case group (n=36) had an umbilical artery cord gas (UACG) pH of 7.10 to 7.15 at delivery, and it was compared with a control group (n=679) where UACG pH was >7.15 (no cases measured an UACG pH <7.10). Parer's five-tier "orange" classifications had a higher specificity (99%; positive likelihood ratio [LR+] 7.1; 95% CI, 1.96–25.5) compared with both three-tier systems: FIGO "pathologic" (87%; LR+ 2.0; 95% CI, 1.1–3.6) and NICHD "category II" (65%; LR+ 1.7; 95% CI, 1.3–2.3). When combined with maternal factors—meconium, chorioamnionitis, and nulliparity—the five-tier system showed the best predictive validity of peripartum asphyxia in neonates as calculated by the area under the curve (AUC) of 0.72 (authors noted that an AUC from 0.7 to 0.8 was acceptable accuracy). This study was limited by the absence of both NICHD "category III" and Parer "red" tracings, and the low number of abnormal tracings limited the calculation of sensitivity.

A 2017 retrospective case-control study (n=202) compared the ability to detect fetal acidemia and assessed interobserver reliability between the international FIGO three-tier and Parer and Ikeda's five-tier FHT systems.[2] The average patient age was 31 years old; 85% were Caucasian. Patients carried singleton term pregnancies at a university hospital in Spain. The acidemic group (n=102) included deliveries with an UACG pH ≤7.1 compared with the control group (n=100) where UACG at delivery had a pH >7.1. FHTs were categorized into both systems. Compared with Parer's five-tier "orange and red" categories, the FIGO 3-tier system's "pathologic" category had a higher sensitivity (44% vs 36%; *P* value not reported) and lower specificity (82 vs 88%; *P* value not reported) to detect fetal acidemia. The five-tier system showed better interobserver reliability when determining concerning FHTs ("orange" or "red", κ: 0.625 vs "pathologic" category, κ: 0.538, *P* values not reported). This study was limited by analysis of a single 30-minute cardiotocography segment.

A 2012 retrospective case-control study (n=97) compared five FHT classification systems, including the NICHD five-tier and Parer and Ikeda's five-tier systems, to evaluate their validity in identifying fetal acidemia.[3] Patients were singleton pregnancies ≥ 35 weeks gestation at a university hospital in Italy. The case group (n=25) had an UACG pH ≤7.15 at delivery compared with the control group (n=72) where pH was >7.15; no cases measured an UACG pH <7.0. All systems had low discriminant validity in predicting UACG pH ≤7.15. Compared with Parer's five-tier, the NICHD three-tier system had a higher sensitivity (67% vs 55%; *P* value not reported) and specificity (92% vs 67%; *P* value not reported) to detect fetal pH ≤7.15. However, the three-tier system categorized 80% of FHTs into "category II." Authors concluded that the five-tier system demonstrated the best tradeoff between sensitivity and specificity. The study was limited by a lack of cases with UACG pH <7.0. A single observer classifying FHTs may have reduced the external validity of the study.

A 2012 retrospective case-control study (n=48) compared the validity of the NICHD three-tier with the

Parer and Ikeda's five-tier systems in identifying fetal acidemia at delivery.[4] Patients carried singleton pregnancies at ≥ 34 weeks gestation, lived in the New York metropolitan area, and had an average age of 31 years old. The case group (n=24) had an UACG pH <7.0 compared with the control group (n=24) which had an UACG pH >7.2 at delivery. All FHTs were categorized into the two systems. Compared with the NICHD three-tier "category III," the five-tier system "orange or red" tracings demonstrated a higher sensitivity for fetal acidemia (79% vs 13%; *P*-value not reported). Both systems had a specificity of 100% for fetal acidemia in these categories; there were no false positives. The study was limited by a small sample size with no cases with UACG pH between 7.0 and 7.2. A single observer classifying FHTs may have reduced the external validity. EBP

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After coronary drug-eluting stent placement, does a longer course of dual antiplatelet therapy lead to decreased thrombotic events?

EVIDENCE-BASED ANSWER

In patients who have undergone coronary drug-eluting stent placement, no difference was observed in thrombotic events and stent failure for patients who received dual antiplatelet therapy (DAPT) for 6 months (short) versus 12 months (standard). Patients receiving long-term (>12 months) DAPT have a significant reduction in stent thrombosis when compared with patients receiving short-term DAPT (≤6 months) but with a higher risk of bleeding. (SOR **A**, meta-analysis of randomized controlled trials). Longer-term DAPT (>12 months) may be reasonable for patients with a low risk of bleeding (SOR **C**, evidence-based guideline).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 meta-analysis of 17 randomized control trials (RCTs; N=46,864) evaluated the efficacy and safety of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with drug-eluting stent (DES).[1] Patients were divided into DAPT treatment duration groups of short term (<6 months), standard term (12 months), and long term (>12 months). Patients included adults (18 years and older) receiving DAPT with aspirin and a platelet $P2Y_{12}$ receptor inhibitor (eg, clopidogrel). Included among the primary outcomes of the study was stent thrombosis. Similar rates of definite or probable stent thrombosis were

noted between standard term (12 months) and short-term (<6 months) DAPT (17 trials, N=46,864; odds ratio [OR] 0.98; 95% confidence interval [CI], 0.59–1.6). Compared with short-term DAPT, long-term DAPT decreased the risk of definite or probable stent thrombosis (4 trials, N=8,857; OR 0.57; 95% CI, 0.34–0.95). The predominant use of clopidogrel in the study limits the generalization of findings to other $P2Y_{12}$ inhibitors. Risk of major bleeding increased with duration of DAPT ≥18 months (16 trials, N=44,152; OR 1.8; 95% CI, 1.3–2.6).

An American College of Cardiology/American Heart Association 2016 clinical guideline focused on the duration of DAPT in patients with coronary artery disease.[2] Six RCTs compared prolonged (18–48 months) with standard length (6–12 months) DAPT, and five RCTS compared short duration (3–6 months) with 12 months DAPT to determine effect on stent thrombosis in patients after DES placement. The largest trial compared patients who had received a DES and were treated with DAPT for 12 months with those who received an additional 18 months of DAPT. Extended DAPT resulted in a 0.4% stent thrombosis compared with 1.4% in the placebo group (hazard ratio 0.29; 95% CI: 0.17–0.48; *P*=.001). The studies did not find any increased risk of stent thrombosis with short-duration DAPT. The guideline authors concluded that in patients with DES after acute coronary syndrome, DAPT for longer than 12 months might be reasonable in patients without high risk for bleeding (strength of recommendation IIb [weak], level of evidence A [high quality from 1 more RCT]). EBP

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Does adding OMT to standard of care help in managing anxiety?

EVIDENCE-BASED ANSWER

Maybe. Adding osteopathic manipulative therapy to standard of care potentially may decrease anxiety symptoms by up to 50% after 10 weeks (SOR: **C**, 2 small, low-quality studies).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 open-label, nonblinded, prospective study (n=26) with no control group investigated the efficacy of adjunctive osteopathic manipulative therapy (OMT) in individuals with generalized anxiety disorder (GAD).[1] This study included patients (mean age 41.4 years old) with a primary diagnosis of GAD who did not achieve remission after 8 weeks of standard treatment (undefined) with a Hamilton Anxiety Rating Score (HAM-A) of mild to moderate anxiety greater than 20 at screening. All participants received five 60-minute individualized sessions based on a full-body OMT assessment with no limit on treatment modality over 8 to 9 weeks. The three validated questionnaires used were the Hamilton Anxiety Rating Scale (HAM-A, range 0–56, >25 indicates severe anxiety), the Beck Anxiety Inventory (BAI range 0–63, >26 indicates severe anxiety), and the Intolerance of Uncertainty Scale (IUS, range 27–135, with no defined severe range). Data were collected seven times total during the intervention: at screening, baseline, and follow-up visits. The patients' mean HAM-A scores decreased from screening to visit 7 (26–11, *P*<.001). Seven patients achieved remission (HAM ≤7). IUS scores also decreased from screening

to final visit (80–67, $P<.0001$). BAI scores did not differ from visit 1 to visit 7 (13–13, $P=.85$). Three patients dropped out, and last observed carried forward analyses found similar results. Limitations included poor internal validity due to the irreproducibility of OMT application and lack of blinding, and over 90% of patients had concurrent major depressive disorder.

A 2021 prospective, controlled study (n=20) looked to determine the effectiveness of OMT in patients with anxiety.[2] Adults over 21 years old who were actively being treated with a psychotropic medication for anxiety and/or depression were randomized into a no-touch control group (n=10) and an OMT group (n=10). Each group received a 60-minute initial visit and seven weekly 30-min follow-up visits with the OMT group receiving soft tissue, counterstrain, muscle energy, and cranial techniques applied to dysfunction based on clinical evaluation. Each visit also included completing a modified Generalized Anxiety Disorder-7 test (GAD-7, scale 0–21) with higher values indicating worse anxiety. Anxiety symptoms assessed using the GAD-7 did not differ between initiation versus completion at week 8 for the control group (22 vs 22; mean difference −0.1; 95% CI, −3.6 to 3.4) but did improve in the OMT group (22 vs 19; mean difference 6.8; 95% CI, 2.9–11). No significant difference existed when anxiety scores were compared between the groups; however, an overall significant improvement in anxiety symptoms was noted in the treatment subgroup. Limitations to the study included a 40% dropout rate in the intervention group (completion n=6) and data compellation after only 8 weeks. EBP

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Which assessment tools are most useful for identifying hospitalized patients at risk of developing severe alcohol withdrawal syndrome?

EVIDENCE-BASED ANSWER

The Prediction of Alcohol Withdrawal Severity Scale is the most accurate risk assessment tool for predicting the development of severe alcohol withdrawal with a positive likelihood ratio (LR+) of 174 and negative likelihood ratio (LR−) of 0.07. Although less sensitive and specific than the Prediction of Alcohol Withdrawal Severity Scale, the Luebeck Alcohol Withdrawal Scale can also accurately predict development of severe withdrawal (SOR: **A**, meta-analysis of cohort studies). The American Society of Addiction Medicine recommends combining assessment tools with an evaluation of individual risk factors (SOR: **C**, expert opinion).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2018 meta-analysis of 14 studies (13 cohort, 1 case control; N=71,295) assessed the diagnostic accuracy of symptoms, signs, and assessment tools for identifying hospitalized patients at risk of developing severe alcohol withdrawal syndrome (SAWS).[1] The studies included adults presenting to alcohol withdrawal management units or hospitals (for any medical reason) with a reasonable index of suspicion for developing alcohol withdrawal. The primary outcome was development of SAWS by discharge, which was defined variably by the individual studies, including presence of delirium

tremens, withdrawal seizure, or clinically diagnosed severe withdrawal. Six studies investigated several composite measures' accuracy in predicting SAWS on presentation, including the Prediction of Alcohol Withdrawal Severity Scale (PAWSS); Cut down, Annoyed, Guilty, Eye opener (CAGE) questionnaire, Luebeck Alcohol Withdrawal Scale (LARS), Alcohol Withdrawal Scale, and other various combinations of signs and symptoms. The PAWSS was the most accurate assessment for identifying patients who would eventually develop SAWS (1 study, n=403; sensitivity 0.99, specificity 0.93; LR+ 174, LR− 0.07). The LARS, though less sensitive and specific than the PAWSS, was also found to accurately predict severe withdrawal (1 study, n=100; sensitivity 0.95, specificity 0.93; LR+ 12, LR− 0.05). Limitations included the limited amount of data for each individual composite, heterogeneity in defining SAWS between studies, and the widespread use of effective treatments to prevent severe alcohol withdrawal, thereby affecting the natural history of alcohol withdrawal.

The 2020 American Society of Addiction Medicine evidence-based clinical practice guideline on alcohol withdrawal management recommended using either PAWS or LARS, along with an assessment of individual risk factors, to determine whether a patient is at risk of developing severe alcohol withdrawal.[2] The guideline authors stated that a high initial score on any validated severity assessment scale could indicate risk of developing severe or complicated withdrawal but warned that these scores should not be the only information used to predict patient risk. They noted that assessment scales are often confounded by outside factors and rely on subjective findings and patient self-reporting. EBP

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What is the average time to reach azoospermia postvasectomy?

EVIDENCE-BASED ANSWER

It is not completely clear. Using the 2012 American Urological Association definition of vasectomy success, the chance of a successful postvasectomy semen analysis (PVSA) is 98% at 90 to 120 days and 100% at >120 days after the vasectomy procedure (SOR: **B**, retrospective studies). Conducting a PVSA is reasonable between 8 and 16 weeks (SOR: **C**, expert opinion).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 retrospective analysis of data using an insurance database examined 87,201 men with one or more postvasectomy semen analysis (PVSA) between 2007 and 2015.[1] This study examined the number of PVSAs after an updated American Urological Association (AUA) guideline provided less stringent criteria for successful vasectomy. Before the guideline published in 2012, successful vasectomy was defined as two consecutive PVSA with azoospermia while the updated recommendation defined successful vasectomy by one PVSA with azoospermia or rare nonmotile sperm (<100,000 nonmotile sperm/mL). This analysis did not specifically examine the time to azoospermia but did provide time frames from vasectomy to PVSA where only one PVSA was needed due to achieving azoospermia. Patients with only one total PVSA (n=55,083) had a mean 104 days between vasectomy and PVSA. Whereas patients with two total

PVSAs (n=24,292) had a mean of 80 days from vasectomy to first PVSA, and patients with 3+ total PVSAs (n=7,826) had a mean of 70 days from vasectomy to first PVSA.

A 2015 retrospective analysis of military service members who had a vasectomy from 2008 to 2013 with one or more PVSAs retrospectively applied the 2012 AUA guidelines compared with their previous institutional protocol requiring repeat PVSAs (N=1,623).[2] Of the identified patients, 55% completed a PVSA (N=895). Using the 2012 AUA guidelines definition of successful vasectomy, if the first PVSA was performed <60 days from the vasectomy, the success rate 87%, compared with if the first PVSA was 61 to 90 days, success rates were 95%, at 91 to 120 days, success was 98%, and at >120 days, success was 100% (ANOVA $P<.001$). Validity was limited by size and the military population not representing the rest of the population regarding health and age.

The 2012 evidence-based AUA vasectomy guidelines define vasectomy success according to a single uncentrifuged sample with azoospermia or rare nonmotile sperm (<100,000 nonmotile sperm/mL).[3] The guideline also stated that timing of first PVSA after vasectomy can occur anytime between 8 and 16 weeks after vasectomy (based on panel consensus). EBP

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What is the best treatment of epistaxis in adults?

EVIDENCE-BASED ANSWER

Effective treatments for epistaxis include topical antiseptic ointment, topical decongestant ointment, chemical cauterization, nasal packing, topical and oral tranexamic acid, endovascular embolization, and surgery. Tranexamic acid seems to produce lower rebleeding rates compared with many other treatment options (SOR: **B**, SR of randomized controlled trials [RCTs] and individual RCTs). For intractable bleeding, embolization and surgical ligation seem to have similar success rates (SOR: **B**, low-quality meta-analysis of case series).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 randomized controlled trial (RCT; n=135) evaluated the effectiveness of topical tranexamic acid (TXA) with external compression alongside two alternative treatments: anterior nasal tampon and external nasal compression.[1] Patients were a median age of 60 years old and presented to the emergency room with anterior epistaxis without current anticoagulation, known bleeding disorder, traumatic epistaxis, or hemodynamic instability (blood pressure <90/60 mmHg and heart rate <100 beats/min). The TXA group received 500 mg tranexamic acid diluted in 5 mL of normal saline administered by atomizer followed by manual external compression for 15 minutes (n=45). The nasal packing received Merocel® nasal tampons placed for 24 hours (n=45). The third group received 5 mL of normal saline administered by atomizer followed by manual external compression for 15 minutes (n=45). At 15 minutes, bleeding was stopped in 91% of TXA group, in 93% of nasal packing group, and in 71% of compression group. TXA and nasal packing significantly outperformed compression in proportion of epistaxis stopped at 15 minutes by 20% (95% CI, 3.6%–35%) and 22% (95% CI, 6.3%–37%), respectively. Rebleeding after 24 hours was

not seen in 87% of TXA group, 73% of nasal packing group, and 60% in compression group. TXA significantly outperformed compression in rebleeding rate by 27% (95% CI, 8.4–43). This RCT was limited by difficulty blinding patients and providers.

A 2018 meta-analysis of six RCTs examined the effectiveness of TXA for epistaxis in 692 adults compared with placebo, no additional intervention, or other hemostatic agents (epinephrine and lidocaine or phenylephrine).[2] TXA was given orally (2 trials) or topically (4 trials). Oral TXA was dosed at 1 g tablets TID for 10 days. Topical TXA was dosed as 15 mL of 10% gel applied locally to fill the nasal cavity or cotton pledgets soaked in injectable form TXA. Hemostatic agents were administered as cotton pledgets soaked in epinephrine (1:100,000) and lidocaine (2%) or 1 mL of phenylephrine (0.5%) poured onto a cotton ball. Oral TXA compared with placebo decreased risk of rebleed within 10 days (2 trials, N=157; risk ratio [RR] 0.73; 95% CI, 0.55–0.96). Topical TXA versus placebo did not demonstrate significant improvement in rebleeding (1 trial; n=68; RR 0.66; 95% CI, 0.41–1.1). Topical TXA demonstrated a better rate of stopping bleeding compared with other hemostatic agents within 10 minutes of application (3 trials, N=460; RR 2.4; 95% CI, 1.9–2.9). This review was limited by the heterogeneity of interventional protocols.

A RCT (n=137) examined the effectiveness of five interventions to prevent further epistaxis in patients with recurrent epistaxis (at least 4 episodes in last month).[3] Patients over 18 years old were included in this study if telangiectasias were observed in Little's area on anterior rhinoscopic evaluation and if they were free of comorbid conditions. Patients were randomized to topical antiseptic ointment (n=26, oxytetracylcine hydrochloride–polymyxin B sulphate BID for 2 weeks), topical decongestant ointment (n=25, ephedrine–naphazoline BID for 2 weeks), chemical cauterization (n=26, silver nitrate sticks after local anesthesia with cotton tamponade and 10% lidocaine for 10 minutes), topical antiseptic ointment plus chemical cauterization (n=30), and topical decongestant ointment plus chemical cauterization (n=30). Patients were contacted at two weeks and one month after treatment by phone to evaluate presence (failure) or absence (success) of at least one episode of epistaxis. No significant difference was identified between the five treatment groups at 15 days ($P=.277$). At 30 days, topical antiseptic ointment alone was less effective than either topical antiseptic ointment with chemical cautery (65% vs 95%, $P<.05$) or topical decongestant ointment plus chemical cautery (65% vs 90%, $P<.05$). At 30 days, topical decongestant ointment alone was less effective than either topical antiseptic ointment plus chemical cautery (68% vs 95%, $P<.05$) and topical decongestant ointment plus chemical cautery (68% vs 90%, $P<.05$). This RCT was limited by reporting and recall bias as outcomes were based on self-reported bleeding.

A systematic review of 44 case series (N=1,664) examined the efficacy and complication rate of endovascular embolization in adults with intractable epistaxis.[4] Epistaxis was attributed to idiopathic, traumatic, neoplastic, postoperative, and coagulopathic causes, with 93% of patients initially receiving nasal packing. Interventions for embolization varied with average follow-up of 17 months (40 studies). Embolization resulted in immediate cessation of bleeding in 87% (95% CI, 84–90) of patients, with a rebleeding rate of 16% (43 studies, N=1,545; 95% CI, 14–20) at a mean of 103 days (7 studies). The complication rate was 14% (95% CI, 9.8–21), with stroke 2.2% (95% CI, 1.5–3.1), visual loss 1.8% (95% CI, 1.2–2.6), and tissue necrosis 2.7% (95% CI, 1.8–4). No predictors were associated with the complication rate. No significant difference in success rate was demonstrated for embolization when compared with surgical ligation (4 studies, N=221; OR 0.86; 95% CI, 0.42–1.75). This review was limited by mostly small retrospective case series, publication bias, and heterogeneity of technology used for embolization. EBP

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Do weighing/measuring techniques versus estimation of blood loss effect on clinical outcome of maternal hemorrhage

EVIDENCE-BASED ANSWER

No, measuring techniques compared with visual estimation of blood loss in patients with postpartum hemorrhage do not improve maternal outcomes of maternal morbidity, blood transfusion, use of fluids to maintain blood pressure, or use of uterotonics to stop bleeding (SOR: **A**, systematic review of randomized controlled trials).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

In 2018, a systematic review of two randomized controlled trials (N=26,281) compared the effectiveness of alternative methods to measure blood loss with visual estimation during the third stage of labor to reduce the adverse consequences of postpartum hemorrhage after vaginal birth.[1] Patients included women (18 years old or any age) who presented for imminent delivery or all women admitted to the maternity unit. Blood loss was quantified using direct measurement with calibrated drapes or collection bags versus visual estimation of blood loss or weighing and measuring blood-soaked materials (gravimetric technique). The primary outcomes included postpartum anemia (hemoglobin [Hgb] <9 mg/dL) and severe maternal morbidity (including coagulopathy, organ failure, and intensive care unit admission). Secondary outcomes included blood loss >500 and 1,000 mL, blood transfusion, use of plasma expanders, use of therapeutic uterotonics, changes in vital signs (such as heart rate, blood pressure, and urine output), further operative procedures (curettage, laparotomy, laparoscopy, surgical exploration, or manual removal of the placenta), hysterectomy for postpartum hemorrhage, infection, maternal predelivery and postdelivery change in Hgb concentration, and maternal death. Moderate-quality evidence showed no difference when using calibrated drapes versus visual estimation for risk of severe maternal morbidity (1 trial, n=2,999; relative risk [RR] 0.82; 95% CI, 0.48–1.4). Secondary outcomes showed no difference between calibrated drapes versus visual estimation and between calibrated drapes and measuring blood-soaked materials for the need for blood transfusion (1 trial, n=5,561; RR 0.82; 95% CI, 0.46–1.5 and 1 trial, n=900; RR 1.0; 95% CI, 0.06–16), use of fluids to maintain blood pressure (1 trial, n=3,122; RR 0.77; 95% CI, 0.42–1.4 and 1 trial, n=900; RR 0.67; 95% CI, 0.19–2.4), or use of uterotonics to stop bleeding (1 trial, n=593; RR 0.87; 95% CI, 0.42–1.8 and 1 trial, n=900; RR 1.01; 95% CI, 0.90–1.1). High-quality evidence showed calibrated drapes superior to measuring blood and blood-soaked materials at detecting blood loss <500 mL (1 trial, n=900; RR 1.9; 95% CI, 1.1–3.1). Potential harms included those produced by invasive methods, such as blood draws, or injection of a substance to quantify blood loss. Both trials were rated as low risk of bias, but the quality of evidence for the predefined outcomes was downgraded because of imprecision or small sample size with few or no events.

In 2019, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion on quantitating blood loss in postpartum hemorrhage.[2] The opinion held that then-current data did not support any one method, measuring, weighing, or visual estimation of blood loss as being superior to the others in improving clinical outcomes. Using measuring techniques was more accurate in the overall quantification of blood loss when compared with visual estimation, but clinical outcomes were unaffected. No strength of recommendation given. EBP

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In pregnant women without history of HTN and without calcium deficiency, does calcium supplementation help with the prevention of hypertensive disorders of pregnancy?

EVIDENCE-BASED ANSWER

In pregnant patients without calcium deficiency, calcium supplementation of 1 g or more per day may reduce the risk of developing hypertension with or without proteinuria by 10%, but does not reduce the risk of preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome (SOR: **B**, systematic review and meta-analysis of low-quality randomized control trials). Guidelines suggest calcium provides little to no benefit in the risk of hypertensive disorders of pregnancy in patients without calcium deficiency (SOR: **B**, practice guidelines based on low-quality to moderate-quality evidence).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2018 systematic review and meta-analysis (27 randomized control trials; N=18,064) evaluated the efficacy of calcium supplementation for the prevention of hypertensive disorders of pregnancy.[1] Patients were at average and high risk for hypertensive disorders of pregnancy and were recruited from countries across the world, with more than half from developing countries. Four trials (N=5,022) enrolled women with adequate dietary calcium intake, defined by trial authors or as a mean daily calcium consumption of at least 900 mg. The intervention included various elemental calcium doses ranging from 500 mg to 2 g per day starting at various gestational ages ranging from 20 to 28 weeks; trials did not specify calcium formulations. Control groups received no treatment or placebo. Primary hypertension-related outcomes included high blood pressure (as defined by trial authors), with or without proteinuria, and preeclampsia; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome was a secondary outcome. Overall, the patients with both adequate and inadequate dietary calcium intake at baseline who received 1 g or more per day calcium supplementation had a 35% reduction in high blood pressure with or without proteinuria (12 trials, N=15,470; relative risk [RR] 0.65; 95% confidence interval [CI], 0.53–0.81) and a 55% reduction in preeclampsia (13 trials, N=15,730; RR 0.45; 95% CI, 0.31–0.65) compared with controls. However, calcium supplementation of 1 g or more per day versus placebo seemed to increase the risk of HELLP syndrome (2 trials, N=12,901; RR 2.7; 95% CI, 1.1–6.8). Subgroup analyses of trials solely recruiting patients with adequate dietary calcium intake demonstrated that calcium supplementation of 1 g or more per day was associated with a 10% reduction in high blood pressure with or without proteinuria (4 trials, N=5,022; RR 0.90, 95% CI, 0.81–0.99) but no difference in preeclampsia (4 trials, N=5,022; RR 0.62, 95% CI, 0.32–1.2) or HELLP syndrome. The reviewers rated the evidence as low quality because of poor methods reporting, incomplete outcome data, possible small study effects or publication bias, and heterogeneity.

In 2020, the World Health Organization made recommendations on prepregnancy calcium supplementation for the prevention of preeclampsia and its complications, based on evidence from a systematic review.[2] The guidelines stated calcium supplementation before or early in pregnancy seemed to provide little or no benefit in the prevention of hypertensive disorders of pregnancy, when compared with placebo or no treatment (low-certainty evidence).

A 2018 World Health Organization evidence-based guideline on the prevention of preeclampsia and its complications recommended 1.5 to 2 g daily calcium supplementation during pregnancy for women with low dietary calcium intake (moderate-certainty evidence).[3] The

recommendation was based primarily on the previously mentioned systematic review.[1] The guideline noted that for women with adequate calcium in their diets, high-dose calcium supplementation probably made little to no difference in the risk of developing preeclampsia. EBP

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What is the impact of Sabbath-keeping on health?

EVIDENCE-BASED ANSWER

Sabbath-keeping is strongly correlated with higher satisfaction in quality and quantity of rest and better social support (SOR: **C**, multiple cross-sectional studies). Sabbath-keeping has no detectible impact on physical health scores (SOR: **C**, large cross-sectional study).

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This clinical quest was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 cross-sectional study (n=1,316) analyzed the relationship between Sabbath-keeping and other forms of rest to mental, physical, and spiritual health in clergy members.[1] Survey responses were collected from active United Methodist Clergy members (aged 24–85 years old). Sabbath-keeping responses were grouped into high Sabbath observance (3–4 days a month), low Sabbath observance (1–2 days a month), and non-Sabbath keeping. Researchers analyzed associations between Sabbath observance and primary outcomes of mental health and physical health, with secondary outcomes of quantity of rest and social support. Mental health was measured by evaluating for depression, anxiety, and burnout by validated measuring tools. Physical health was measured by body mass index and physical health functioning. Non-Sabbath observers were more than twice as likely to have scores qualifying for depression on the Patient Health Questionnaire 9 compared with high Sabbath-keepers (12% vs 5%, $P<.001$). A significant but clinically small decrease was observed in those scoring moderate/high anxiety on General Anxiety Disorder 7 questionnaire between non-Sabbath keepers and high Sabbath-keepers (5% vs 3%, $P=.042$). High Sabbath-keepers also reported less burnout (33% vs 43%, $P=.001$). In addition, high Sabbath-keepers reported more physical rest compared with the Sabbath nonobservers with an average of 2.5 more vacation days, 24 minutes more sleep a night, and 1.7 hours more spent on relaxing activities per week ($P<.001$). High Sabbath-keepers also were almost twice as likely as Sabbath nonobservers to report that they "always" received the social support they needed (31% vs 17%, $P<.001$). However, after controlling for social support and other forms of rejuvenation, no significant differences were observed between Sabbath-keeping and lower scores for depression, anxiety, and burnout. Sabbath-keeping did not have significant associations with measures of physical health.

A 2014 cross-sectional study (n=5,411) examined the correlation between Sabbath observance and mental and physical health.[2] Results were obtained from self-reported surveys taken by adult North American Seventh-Day Adventist Christians. Sabbath observance was measured by how much participants abstained from secular activities on the seventh day (Sabbath), indicated on a 6-point scale from "every Sabbath" to "never," with higher scores signifying more Sabbath observance. Mental health scores were measured by a validated questionnaire tool. A significant but very weak

association was noted between higher Sabbath-keeping scores and higher mental health scores (r=0.11, $P<.01$). This finding was of questionable significance given the weakness of association. No correlation was noted between Sabbath-keeping and physical health scores (r=0.0, $P>.05$).

A 2015 cross-sectional study (n=296) assessed the impact of Sabbath-keeping on satisfaction with the quantity and quality of rest in life.[3] Mental health clinicians and graduate students of Judeo-Christian backgrounds aged 18 to >70 years old were included and responses were gathered by an online survey. Sabbath observance was assessed by the survey question "at least 1 day a week off from work" and responses categorized into groups "yes," "varied," and "no." Quality and quantity of rest was measured by a 1 to 7 Likert scale, with higher scores representing better satisfaction. Rest quality and quantity scores were significantly higher in the yes group compared with the varied and no groups (4.7 vs 4.1 vs 3.5, respectively, $P<.01$). EBP

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Does regular exercise help significantly reduce blood pressure in adults diagnosed with hypertension within the general population?

EVIDENCE-BASED ANSWER

Yes. The implementation of a regular aerobic exercise regimen reduces systolic blood pressure by 8 mmHg and diastolic blood pressure by 5 mmHg in adults with hypertension (SOR: **C**, meta-analysis of small, randomized controlled trials [RCTs]). A regimen of moderate-intensity aerobic exercise completed three days per week for 12 weeks reduces mean ambulatory systolic blood pressures by approximately 7 mmHg in adults with resistant hypertension (SOR: **C**, small, single-blinded RCT).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systemic review and meta-analysis of 37 randomized controlled trials (RCTs; N=1,813) compared systolic and diastolic blood pressure changes in adult hypertensive patients treated with or without an aerobic exercise regimen.[1] Studies included both men and women 18 years old or older with hypertension. The average age of patients ranged from 30 to 70 years old. No limitation was noted on concurrent use of antihypertensive medications or duration of aerobic exercise

programs. Included studies implemented any regular aerobic exercise program, with walking, running, cycling, dance, and swimming most evaluated. Researchers excluded studies implementing diet or lifestyle changes, nonaerobic exercises (such as resistance training), and nonexperimental or single-arm designs. Only 31 studies reported the intensity of exercises, which was measured by maximal oxygen consumption, maximal heart rate, perceived exertion rating, and heart rate reserve. Twenty-three studies evaluated exercise programs completed three times per week, with the rest ranging from 2 to 5 times per week. Studies most commonly implemented 12-week exercise programs, but duration ranged from 4 to 37 weeks. Primary outcomes were a reduction of systolic and diastolic blood pressures. Regular aerobic exercise reduced systolic blood pressure by 8.3 mmHg (95% CI, 6.5−10) and diastolic blood pressure by 5.2 mmHg (95% CI, 4.1−6.2). Moderate- and vigorous-intensity exercise effectively reduced both systolic and diastolic blood pressure, whereas low-intensity exercise did not (**TABLE**). All exercise program frequencies (2, 3, or 4 or more times/wk) and durations (4 to 24 or more weeks) resulted in blood pressure reductions. This meta-analysis was limited by a low number of studies evaluating low-intensity exercise programs and lack of patient-oriented outcomes.

A 2021 single-blinded RCT (n=53) compared mean systolic and diastolic blood pressure changes in adults with resistant hypertension after 12 weeks of usual care with and without a moderate-intensity aerobic exercise training program.[2] Adults 40 to 75 years old (mean age 60 years old, 45% women) with resistant hypertension were recruited from two outpatient hypertension clinics in Portugal. Resistant hypertension was defined as 24-hour mean ambulatory blood pressures of greater than 130 mmHg (or >135 mmHg during daytime hours) while taking three antihypertensive medications including a diuretic or hypertension controlled with four antihypertensive medications. Exclusion criteria included any changes in hypertensive medications in the last three months, secondary hypertension, or end-organ damage. The aerobic exercise training program consisted of three supervised 40-minute sessions per week, beginning with 20 minutes of walking or cycling at 50% maximal oxygen

TABLE. Effects of exercise intensity, frequency, and duration on blood pressure reduction in 1,813 adults with hypertension[1]

	No. of Studies	No. of patients (n)	Decrease in systolic blood pressure (95% CI)	Decrease in diastolic blood pressure (95% CI)
Intensity				
Low	2	36	2.93 (–1.39 to 7.25)	1.62 (–0.28 to 3.52)
Moderate	22	1,146	**8.97 (6.84–11.11)**	**5.75 (4.32–7.18)**
High	9	443	**6.85 (1.66–12.03)**	**4.36 (2.79–5.94)**
Frequency				
2 times per week	7	197	**6.10 (3.37–8.83)**	**4.38 (1.66–7.09)**
3 times per week	26	1,361	**9.16 (6.66–11.66)**	**5.55 (4.23–6.87)**
≥4 times per week	6	256	**6.96 (4.64–9.27)**	**4.50 (2.20–6.80)**
Duration				
4–7 weeks	3	218	**3.04 (0.95–5.14)**	**3.58 (2.39–4.77)**
8–11 weeks	7	454	**9.12 (4.16–14.09)**	**5.42 (2.89–7.95)**
12–23 weeks	22	976	**8.77 (6.49–11.06)**	**4.84 (3.28–6.40)**
≥24 weeks	7	165	**8.24 (6.27–10.77)**	**7.15 (5.15–9.14)**

consumption and working up to 40 minutes at 70% maximal oxygen consumption as tolerated. Both the exercise and the control groups received "usual care" education on lifestyle changes and optimal medication management by their physicians. The primary outcome was the reduction in 24-hour ambulatory systolic blood pressure as measured at baseline and 48 hours after the last training session. Exercise reduced 24-hour mean ambulatory systolic blood pressure by 7.1 mmHg (95% CI, 1.4−13; P=.02) and diastolic blood pressure by 5.1 mmHg (95% CI, −7.9 to −2.3; P=.001). Exercise also reduced ambulatory daytime systolic blood pressure by 8.4 mmHg (95% CI, 2.5–14; P=.006) and diastolic blood pressure by 5.7 mmHg (95% CI, 2.4–9.0; P=.001). Reported side effects in the exercise arm included dizziness and musculoskeletal soreness during the initial weeks of exercise. No severe adverse events occurred. Study limitations included small sample size, lack of subgroup analysis, and absence of patient-oriented outcomes. EBP

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Is aspirin use in pregnancy associated with increased bleeding risks?

EVIDENCE-BASED ANSWER

Hastie R, Tong S, Wikström AK, Sandström A, Hesselman S, Bergman L. Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study. Am J Obstet Gynecol. 2021;224(1):95.e1-95.e12. doi: 10.1016/j.ajog.2020.07.023.

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This retrospective cohort study used data from the Swedish national pregnancy registry to examine bleeding outcomes in women taking low-dose aspirin in pregnancy for preeclampsia prevention. Typical low-dose aspirin in Sweden was 75 mg daily. The registry captured data on 90% of all deliveries nationally from 2013 to 2017 (N=313,624), 1.3% (n=4,088) of whom self-reported taking aspirin at any visit during prenatal care. Patients were excluded for missing records (n=11,254) or because they were taking low-molecular-weight heparin or SSRIs that could theoretically increase bleeding risk (n=10,735). The authors used inverse probability treatment weighting and propensity scoring to account for potential cofounding because aspirin is given only to pregnant women at inherently higher risk. Compared with those not taking aspirin, women on aspirin were more likely to experience intrapartum bleeding (2.9% vs 1.5%, odds ratio [OR] 1.63; 95% CI, 1.30–2.05, number needed to harm [NNH]=167), postpartum hemorrhage (10.2% vs 7.8%, OR 1.23; 95% CI,

1.08–1.39, NNH=42), postpartum hematoma (0.4% vs 0.1%, OR 2.22; 95% CI, 1.13–4.34, NNH=333), and neonatal intracranial hemorrhage (0.07% vs 0.01%, OR 9.66; 95% CI, 1.88–49.48, NNH=1,667). No excess risk for nonobstetric bleeding was noted. After stratifying by mode of birth, the excess postpartum hemorrhage risk from aspirin remained associated with vaginal but not cesarean birth. After exclusion of women who developed preeclampsia, the small excess neonatal intracranial hemorrhage risk was no longer seen. The authors called for caution with universal aspirin use in pregnancy. The observational study was limited by residual confounding. Benefits of aspirin use to prevent preeclampsia were not outcomes in this study. Randomized trials and other meta-analyses have not noted similar bleeding risks.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching guidelines by USPSTF, ACOG, and NICE. The associated systematic reviews for these guidelines, those from Cochrane, and landmark randomized controlled trials including the ASPRE trial were reviewed.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	No	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: In a real-world cohort, aspirin use in pregnancy seemed to be associated with a small increased risk for postpartum hemorrhage and postpartum hematoma but not antepartum bleeding. It may also be associated with a small risk in neonatal intracranial hemorrhage, although numbers were small. The study was limited by its observational nature and residual confounding. Similar associations have not been seen in randomized trials. EBP

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What are the rates of adverse events in patients who receive mRNA COVID vaccines?

EVIDENCE-BASED ANSWER

Local and systemic adverse reactions, such as pain at injection site, fatigue, and headache, occur in the majority of adults receiving both the mRNA-1273 vaccine (Moderna) and the mRNA BNT162b2 vaccine (Pfizer) in the first seven days after injection. Adverse events in the 28 days after injection related to vaccination occur in 8.2% and 20.7% of patients who receive the mRNA-1273 and mRNA BNT162b2 vaccine, respectively. Serious adverse events related to either vaccine are rare, occurring in less than 0.1% of patients (SOR: **A**, consistent randomized controlled trials).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

In 2021, a multicenter randomized controlled trial (RCT; n=30,420) in the United States evaluated the safety and side effects of the mRNA-1273 vaccine, manufactured by Moderna, compared with placebo.[1] Eligible participants were 18 years old or older without a known history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, but whose circumstances put them at an appreciable risk of symptomatic SARS-CoV-2 infections. Reasons for exclusion included recent illness within 72 hours, pregnancy, breastfeeding, contraindications to intramuscular vaccination or phlebotomy, or having an immunocompromised state. The

TABLE 1. List of unsolicited adverse events to mRNA-1273 vaccine (Moderna) within 28 says of second vaccination[1]

Injection	Nervous system disorders, n (%)	Respiratory, thoracic and mediastinal disorders, n (%)	Gastrointestinal disorders, n (%)	Musculoskeletal disorders, n (%)	General disorders, n (%)	Hypersensitivity reactions,[a] n (%)
mRNA-1273 both doses (n=15,185)	684 (4.5)	536 (3.5)	478 (3.1)	671 (4.4)	1,006 (6.6)	233 (1.5)
Placebo both doses (n=15,166)	622 (4.1)	583 (3.8)	440 (2.9)	617 (4.1)	622 (4.1)	166 (1.1)

Note: The most common adverse events in each disorder category are as follows: headache (nervous system); cough and oropharyngeal pain (respiratory, thoracic, and mediastinal); nausea, vomiting, and diarrhea (gastrointestinal); arthralgia and myalgia (musculoskeletal); fatigue and injection site pain (general disorders). [a] Only one patient in both groups experienced an anaphylactic hypersensitivity reaction.

intervention group received the mRNA-1273 vaccine (0.5 mL containing 100 μg) administered by injection into the deltoid muscle by a two-dose regimen in the same arm, 28 days apart. The control group was given saline placebo by the same protocol. Safety assessments on all patients included monitoring solicited side effects for seven days after each injection, unsolicited adverse events for 28 days after each injection, and medically attended or serious adverse events occurring anytime during the duration of the trial. During the seven days after injection, local adverse reactions (pain, erythema, axillary swelling, or injection site swelling) occurred in 86.4% of the mRNA-1273 group and 19.3% of the placebo group. Systemic adverse events (fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, or chills) occurred in 67.0% of the vaccine group and 39.6% of the placebo group. Unsolicited adverse events (**TABLE 1**) deemed by the research team to be related to vaccination in the 28 days after injections occurred in 8.2% of the vaccine group, and 4.5% of patients receiving placebo. Serious adverse events occurred in <0.1% of patients in both treatment arms (**TABLE 2**). Approximately 0.3% of the mRNA-1273 arm and 0.5% in the placebo arm did not receive the second dose because of adverse events. Two deaths occurred in the vaccine group compared with three deaths in the placebo group, all of which were deemed unrelated to the study. Limitations of the study include short duration of safety follow-up period (28–89 days), unclear definitions of adverse event severities, pharmaceutical company funding, and lack of CIs or direct statistical comparison between the treatment and control groups within the safety data set.

In 2020, a multicenter RCT (n=43,252), including participants from North and South America, Africa, and Europe, examined safety and types of adverse events after administration of the BNT162b2 vaccine, manufactured by Pfizer, compared with placebo.[2] Eligible patients were persons 16 years old or older who were healthy or had stable chronic medical conditions, such as HIV, hepatitis B, or hepatitis C infection. Exclusionary criteria included a history of SARS-CoV-2 infection, current treatment with immunosuppressive therapy, or a new diagnosis of an immunocompromising condition. Patients were randomly assigned to either 30 μg BNT162b2 or saline placebo for two injections, 21 days apart, delivered to their deltoid muscle. Safety was assessed with solicited, specific local or systemic adverse events, or use of antipyretic or pain medication

TABLE 2. Summary of unsolicited adverse events to mRNA-1273 vaccine (Moderna) within 28 days of second vaccination[1]

Injection	All, n (%)	Related, n (%)	Related severe, n (%)	Related serious, n (%)	Any related leading to withdrawal, n (%)
mRNA-1273 both doses (n=15,185)	3,632 (23.9)	1,242 (8.2)	71 (0.5)	6 (<0.1)	18 (0.1)
Placebo both doses (n=15,166)	3,277 (21.6)	686 (4.5)	28 (0.2)	4 (<0.1)	15 (0.1)

TABLE 3. Summary of unsolicited adverse events in >16-year-old recipients of the BNT162b2 vaccine (Pfizer) within 6 months of vaccination[2]

Injection	Any, n (%)	Any related, n (%)	Any serious, n (%)	Any related serious, n (%)	Any related leading to withdrawal, n (%)
BNT162b2 (n=21,621)	5,770 (26.7)	4,484 (20.7)	126 (0.6)	4 (0.0)	16 (0.1)
Placebo (n=21,631)	2,638 (12.2)	1,095 (5.1)	111 (0.5)	0 (0)	9 (0.0)

within seven days of each dose from a subset of 8,183 patients who were provided an electronic diary. Unsolicited adverse events through one month after the second dose and unsolicited severe adverse events through six months after the second dose were collected from all patients. At time of publication, event data through approximately 14 weeks from the second dose were reported. Solicited local and systemic adverse reactions in the vaccination group were higher than in the placebo group, with pain at injection site (age 16–55 years old: 83% vs 14%; age >55 years old: 73% vs 9%), fatigue (age 16–55 years old: 47% vs 33%; age >55 years old: 34% vs 23%), and headache (age 16–55 years old: 42% vs 34%; age >55 years old: 25% vs 18%) most commonly reported after the first injection. Adverse events reported within seven days after the second injection were similar. Unsolicited adverse events deemed related to study intervention within six months after the second dose occurred in 20.7% of BNT162b2 group and 5.1% of the placebo group (**TABLE 3**). Few patients in either group had severe adverse events or events leading to withdrawal from the trial. Four related serious adverse events were reported among the BNT162b2 group (right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, shoulder injury related to vaccine administration, and right leg paresthesia), which were not seen in the placebo group. Two BNT162b2 recipients died, as did four placebo recipients, but none were considered related to the vaccine or placebo. Limitations of this study included a short duration of safety follow-up, the possibility of not detecting rare adverse events because of sample size, and funding by the vaccine manufacturers. EBP

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Is vaginal hyaluronic acid effective in reducing symptoms of genitourinary syndrome of menopause?

EVIDENCE-BASED ANSWER

Perhaps. Vaginal hyaluronic acid (HA) may reduce genitourinary menopausal symptoms more than vaginal vitamin E therapy (SOR: **C**; small randomized controlled trial [RCT]). HA seems as effective or more effective than placebo and some vaginal estrogen dosing regimens but not all (SOR **B**; systemic review of heterogeneous RCTs).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2012 single-center randomized controlled trial (RCT; n=40) examined the effectiveness of hyaluronic acid (HA) for atrophic vaginitis compared with vitamin E vaginal tablets.[1] Patients were women 45 to 65 years old with postmenopausal symptoms for at least 1 year, or an FSH >40 mIU/mL, and a normal recent pap smear. Patients were excluded for recent genital infections or abnormalities, recent use of sex hormones or phytoestrogens, and undiagnosed vaginal bleeding. One group received 5 mg HA vaginal suppositories and the other received 1 mg vitamin E vaginal suppositories. Suppositories were administered daily for the first two weeks, followed by three times weekly for the remaining six weeks. The primary outcome was improvement in the Composite Score of Vaginal Symptoms (CSVS), with patients self-scoring symptoms on a 0 to 3 point scale for each category of vaginal dryness, soreness, irritation, and dyspareunia. Higher scores indicated more severe symptoms. HA significantly improved vaginal symptoms from pretreatment to post-treatment (mean composite scores 4.7 vs 0.15, $P<.01$). HA was more effective than the vitamin E (mean difference [MD] 0.5; 95% CI, 0.95–0.46) after six weeks. No reported side effects were observed of either intervention. Limitations included recruitment at a single center.

A 2021 systematic review of 5 RCTs (N=335) evaluated the efficacy of vaginal HA in postmenopausal women with vaginal atrophy.[2] The review included postmenopausal female patients from Turkey, China, Iran, Brazil, and Italy, with an age range of 45 to 70 years old. Inclusion criteria were studies evaluating menopausal or postmenopausal patients and comparing HA with a control group of vaginal estrogen, another vaginal hormone, or placebo. Exclusion criteria included patients with increased risk of thrombosis, chronic diseases, cancer, or use of hormones or intravaginal medications before the study. Studies ranged from 3 to 8 weeks in duration. Four of five studies showed no difference or superior relief of symptoms in the HA group compared with the control. Two studies found no significant difference between the HA group and the comparison hormone groups in relieving vaginal symptoms. One of these "negative" studies (n=133) compared estriol vaginal cream (0.5 g every 3 days for 10 doses) with HA vaginal gel (5 g every 3 days for 10 doses). The second "negative" study (n=68) compared daily estradiol cream (2.5 g daily for 3 weeks) with HA cream (twice weekly for 3 weeks). Another study (n=36) reported daily HA to be superior to placebo for vaginal itching and burning but not dryness; statistical reporting was not provided for this study. Another study (n=56) showed significantly greater improvement in patient-reported symptoms as measured by the CSVS score in the HA (5 mg cream daily) compared with conjugated estrogen cream (0.625 mg daily for 14 days then twice weekly for 6 weeks) with an MD of 1.5 (95% CI, 0.54–2.5). Only one study (n=42) found HA (5 mg daily for 8 weeks) to be inferior to estradiol (25 mg tablet daily for 14 days then twice weekly for 6 weeks) as measured by the CSVS (MD 1.19; 95% CI, 0.28–2.1). No treatment-related side effects were observed in any of the studies. Meta-analysis was not possible because of marked heterogeneity of study design and outcomes. EBP

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Can the evaluation of cardiovascular risk factors in postmenopausal women prolong life?

EVIDENCE-BASED ANSWER

Evaluation of cardiovascular risk factors in postmenopausal women such as hypertension, elevated cholesterol, increased waist circumference, smoking, and diabetes identifies those at increased risk of cardiovascular events (SOR: **C**, cross-sectional study). Applying established guidelines from the American Heart Association can minimize these cardiovascular risk factors (SOR: **C**, case series study). However, this may not have a significant effect on all-cause mortality (SOR: **C**, large prospective cohort study).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2018 population-based, prospective parallel cohort study (n=107,491) examined the effectiveness of screening postmenopausal women for cardiovascular disease (CVD).[1] Patients born between 1936 and 1951 were identified using the Danish Civil Registration System. Of these, women born in the years 1936, 1941, 1946, and 1951 within the Viborg municipality were invited to become part of a cardiovascular screening group (n=1,984), whereas the remainder (n=105,507) constituted the control group. Patients were followed for a median period of 3.3 years. Patients underwent comprehensive cardiovascular screening, including screening for abdominal aortic aneurysm by ultrasound as defined by an anteroposterior aortic diameter ≥30 mm, peripheral artery disease (PAD) as defined by an ankle brachial pressure index <0.9 or ≥1.4, carotid plaque using ultrasound as defined by a focal structure that encroached into the arterial lumen of ≥0.5 mm or ≥50% of the surrounding vessel, hypertension (HTN) as defined by blood pressure (BP) ≥160/100 mmHg via multiple blood pressure measurements, dyslipidemia based on nonfasting total cholesterol ≥135 mg/dL, atrial fibrillation if an abnormal rhythm was noted on Doppler during PAD screening, and verified by electrocardiogram, and DM-2 as defined by HbA1c ≥6.5%. The primary outcome was all-cause mortality. The secondary outcome was CVD morbidity at three years. No difference in all-cause mortality was noted between the two groups (adjusted hazard ratios [aHRs] 0.89; 95% CI, 0.71–1.12). In addition, no significant differences were noted in CVD morbidity, including myocardial infarction (aHR 1.26; 95% CI, 0.52–3.07), ischemic heart disease (aHR 0.72; 95% CI, 0.49–1.05), PAD (aHR 1.07; 95% CI, 0.49–2.31), ischemic stroke (aHR 1.20; 95% CI, 0.78–1.85), and hemorrhagic stroke (aHR 0.39; 95% CI, 0.05–2.94) between the groups when adjusted for age, hospitalization before start, and previous use of antiplatelet therapy.

A 2012 cross-sectional study (n=575) examined the association between postmenopausal women and CVD risk factors clustered into metabolic syndrome (MS).[2] Patients 45 to 54 years old in the Czech Republic were selected from the general health company registry. Patients were categorized into three groups of menopausal status based on the stages reproductive aging workshop criteria: premenopausal as the control group (n=351, less than 33 days since last menstrual period), perimenopausal (n=95, 33–365 days since last menstrual period), and postmenopausal (n=129, more than 365 days since their last menstrual period). Patients with surgical menopause or on hormone replacement therapy were excluded. Cardiovascular risk factors were identified according to national cholesterol education program 2001 guidelines and the Harmonizing Metabolic Syndrome 2009 criteria. Postmenopausal women with no medications for DM, HTN, or hyperlipidemia (HLD) showed a significantly higher rate for MS than premenopausal women, when adjusted for age (odds ratio [OR] 2.3; 95% CI, 1.2–4.3). Compared with premenopausal women, postmenopausal women treated for DM and HTN demonstrated a significantly higher risk for MS (OR 2.0; 95% CI, 1.1–3.6) and those treated for any combination of HTN, DM, or HLD continued to show an increased risk (OR 2.0; 95% CI, 1.1–3.6). A significant effect was also noted on lipid profiles in postmenopausal women compared to premenopausal women when adjusted for age, total cholesterol (effect size [ES] 0.27; 95% CI, 0.05–0.48), non-HDL cholesterol (ES 0.32; 95% CI,

0.09–0.55), and LDL cholesterol (ES 0.24; 95% CI, 0.04–0.44).

A 2009 case series (n=2,789) investigated the effectiveness of applying professional guidelines for cardiovascular risk reduction in postmenopausal women.[3] Patients had a mean age of 56.7 years old from 18 menopause clinics in Hungary. All patients had two or more cardiovascular risk factors that included cigarette smoking, HTN (blood pressure >140/90 mmHg or on antihypertensive medication), low HDL cholesterol (HDL-C <40 mg/dL), family history of premature coronary artery disease (male first-degree relative 55 years old or younger, or female first-degree relative 65 years old or younger), age 55 years old or older, and a history of diabetes. Cardiovascular risk was measured using the Framingham risk assessment and the systemic coronary risk evaluation (SCORE) methods. Laboratory and BP values were measured at the start and end of the trial. Goals of treatment followed the 2002 American Heart Association guidelines for primary prevention of CVD and stroke, which included complete smoking cessation, BP <140/90 mmHg, HDL-C >50 mg/dL, waist circumference <35 in, and normal fasting plasma glucose levels (<110 mg/dL). Patients were followed every four months for one year. Significant differences were noted in total cholesterol between the start and end of the study (start 6.08 mmol/L vs end 5.03 mmol/L, $P<.0001$), LDL (start 3.63 mmol/L vs end 2.76 mmol/L, $P<.0001$), triglycerides (start 1.65 vs end 1.34 mmol/L, $P<.0001$), fasting plasma glucose (start 5.69 mmol/L vs end 5.38 mmol/L, $P<.0001$), systolic BP (start 133.58 mmHg vs end 127 mmol/L, $P<.0001$), and diastolic BP (start 85.60 mmHg vs end 80.64 mmol/L, $P<.0001$), but no significant difference was noted in HDL (start 1.67 mmol/L vs end 1.71 mmol/L). Framingham and SCORE assessments showed decreased cardiovascular risk compared with baseline (no data given, $P<.0001$). EBP

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Do SGLT2 inhibitors slow progression of chronic kidney disease?

EVIDENCE-BASED ANSWER

Yes. SGLT2 inhibitors slow progression to the composite outcome of chronic dialysis, kidney transplantation, or renal death by 33% in patients with type 2 diabetes mellitus (DM-2) (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). The kidney-protective effects of SGLT2 inhibitors are also seen in patients without DM-2 (SOR: B, single RCT).

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The following methods statement is included under the Evidence-Based Answer before the Evidence Summary: This clinical quest was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 meta-analysis of four randomized controlled trials (RCTs) assessed the effect of empagliflozin (1 trial, n=7,020), canagliflozin (2 trials, N=14,543), and dapagliflozin (1 trail, n=17,160) on major kidney outcomes in adult patients with type 2 diabetes mellitus (DM-2).[1] One of the canagliflozin trials was the first to assess the effect of an SGLT2 inhibitor on a primary kidney outcome in patients with established diabetic kidney disease, while the remaining trials were primarily cardiovascular outcome trials of SGLT2 inhibitors with secondary renal endpoints. The proportion of patients with baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 varied, as did the proportion with urine albumin creatinine ratio higher than 30 mg/g (**TABLE 1**). Standard dosing of a single SGLT2 inhibitor was compared with placebo, and median follow-up was greater than two years (range, 2.4–4.2 years). SGLT2 inhibitors reduced the combined risk of chronic dialysis, kidney transplantation, or death due to kidney disease by 33% compared with placebo. SGLT2 inhibitors also reduced the risk of other major kidney outcomes (**TABLE 2**). Subgroup analysis for the outcome of substantial loss of kidney function, end-stage kidney disease, or renal death showed a similar risk reduction for patients with baseline eGFR <60 mL/min/1.73 m^2. This meta-analysis was limited in that kidney endpoints were defined and reported differently across the studies.

A 2020 double-blind RCT (n=4,304) compared dapagliflozin with placebo in reducing the risk of renal disease progression in adult patients with chronic kidney disease (CKD).[2] Patients had an eGFR of 25 to 75 mL/min/1.73 m^2 and a urine albumin/creatinine ratio of 200 to 5,000 mg/g. In contrast to earlier studies, 33% of patients in this trial did not have DM-2, and 15% had an eGFR below 30 mL/min/1.73 m^2. Dapagliflozin 10 mg daily

TABLE 1. Baseline renal function in meta-analysis of SGLT2 inhibitors versus placebo for renal protection (4 studies, N=38,723)[1]

	Empagliflozin trial (N=7,020)	Canagliflozin trial (N=10,142)	Dapagliflozin trial (N=17,160)	Canagliflozin trial (N=4,401)	Totals (4 trials)
Baseline estimated glomerular filtration rate (mL/min/1.73 m^2)					N=38,718[a]
≥90	1,538 (22%)	2,476 (24%)	8,162 (48%)	0	12,176 (31%)
60 to <90	3,661 (52%)	5,625 (56%)	7,732 (45%)	1,809 (41%)	18,827 (49%)
45 to <60	1,249 (18%)	1,485 (15%)	1,265 (7.4%)	1,279 (29%)	5,278 (14%)
<45	570 (8.1%)	554 (5.5%)	0	1,313 (30%)	2,437 (6.3%)
Baseline urine albumin creatinine ratio (mg/g)					N=38,230[a]
<30	4,171 (59%)	7,007 (69%)	11,644 (68%)	0	22,822 (60%)
30–300	2,013 (29%)	2,266 (22%)	4,030 (24%)	0	8,309 (22%)
>300	769 (11%)	760 (7.5%)	1,169 (6.8%)	4,401 (100%)	7,099 (19%)

[a] Excludes patients missing baseline data.

TABLE 2. Efficacy of SGLT2 inhibitors versus placebo for renal protection

Meta-analysis including patients with type 2 diabetes mellitus[1]				
	No. of trials	**No. of patients**	**Relative risk**	**95% CI**
All patients				
Chronic dialysis, kidney transplantation, or death due to kidney disease	4	38,723	0.67	0.52–0.86
End-stage kidney disease[a]	4	38,723	0.65	0.53–0.81
Substantial loss of kidney function[b], end-stage kidney disease[a], or renal death	4	38,723	0.58	0.51–0.66
Baseline eGFR <60 ml/min/1.73m2				
Substantial loss of kidney function[b], end-stage kidney disease[a], or renal death	4	7,697	0.63	0.52–0.77
RCT including patients with and without type 2 diabetes mellitus				
	No. of trials	**No. of patients**	**Hazard ratio**	**95% CI**
All patients				
Sustained loss of kidney function[c], end-stage kidney disease[d], or death from renal or cardiovascular causes	1	4,304	0.61	0.51–0.72
Sustained loss of kidney function[c], end-stage kidney disease[d], or renal death	1	4,304	0.56	0.45–0.68
Sustained loss of kidney function[c]	1	4,304	0.53	0.42–0.67
End-stage kidney disease[d]	1	4,304	0.64	0.50–0.82
Patients without type 2 diabetes				
Sustained loss of kidney function[c], end-stage kidney disease[d], or death from renal or cardiovascular causes	1	4,304	0.50	0.35–0.72

[a] Defined most commonly as chronic dialysis, kidney transplantation, or sustained estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2. [b] Defined as sustained doubling of serum creatinine or sustained 40% decline in eGFR. [c] Defined as sustained 50% decline in eGFR. [d] Defined as chronic dialysis, kidney transplantation, or sustained eGFR lower than 15 mL/min/1.73 m^2.

was compared with placebo, and median follow-up was 2.4 years. The primary outcome was the composite of sustained loss of kidney function, progression to end-stage kidney disease, and death from renal or cardiovascular causes. Randomization was stratified according to the diagnosis of DM-2 and level of albuminuria. Secondary outcomes included the composite renal outcome of sustained loss of kidney function, progression to end-stage kidney disease, and renal death, along with the individual components. Dapagliflozin significantly decreased the primary composite outcome, the composite renal outcome, and the individual components of sustained loss of kidney function and progression to end-stage kidney disease (**TABLE 2**). The effect of dapagliflozin on the primary composite outcome was consistent across prespecified subgroups defined by the presence or absence of DM-2 and the severity of CKD. An independent data monitoring committee recommended the trial be discontinued early because of clear efficacy. EBP

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The authors declare no conflicts of interest.

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