Syllabus for Essential Evidence 2023
North Dakota Academy of Family Physicians
January 16, 2023

Learning Objectives

Discuss recent research important to family physicians and other primary care clinicians for updating their diagnostic and treatment approaches to common medical conditions. Objectives for each presentation are listed at the beginning of each talk. Each talk is based on a literature review of recent research studies. Evidence sources include InfoPOEMs®, PubMed and Cochrane systematic reviews.

Faculty

Henry C. Barry, MD, MS is a Professor Emeritus of Family Medicine in the College of Human Medicine at Michigan State University. After graduating from the University of Maryland, he completed his family medicine residency at St. Lawrence Hospital in Lansing, Michigan and completed a master's in Clinical Research Design and Statistical Analysis at the University of Michigan School of Public Health. For 25 years, as one of the original "POETs," he and colleagues have generated over 6000 POEMs – Patient Oriented Evidence that Matters – short critical summaries of original research on topics relevant to primary care physicians.

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Faculty Disclosure Statement

Dr. Barry is paid for writing InfoPOEMs®. Dr. Ferenchick has no relevant financial relationship or interest with a proprietary entity producing health care goods or services.

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Musculoskeletal Potpourri

Henry C. Barry, MD, MS

Objectives: At the end of this session, the participant will be able to:

- Describe diagnostic strategies for common musculoskeletal disorders
- Describe effective approaches in managing musculoskeletal pain

Diagnosis

While clinical findings can be very useful in diagnosing some conditions, such as lateral epicondylitis, it is of limited use in others. In the following studies, recall that a positive likelihood ratio (LR) of 10 or greater and that negative LRs less than 0.1 are ***very*** helpful. LRs near 1 are useless.

1. Useful signs and symptoms for diagnosing hip osteoarthritis

Clinical question: What clinical signs and symptoms are useful for diagnosing radiographic-based hip osteoarthritis in adults?
Study design: Systematic review **Setting:** Various (meta-analysis)
Synopsis: In the absence of a more reliable gold standard of diagnosis, these investigators wished to evaluate the accuracy of clinical findings in determining the prevalence of radiographic OA among adults presenting with hip pain or groin pain. Two individuals independently searched multiple databases, including PubMed, MEDLINE, and CINAHL, as well as reference lists of previous review articles for studies describing clinical findings in patients with hip pain or groin pain. Studies were assessed for risk of bias using a standard scoring tool, and only level 1 and 2 studies (N = 6, reporting data from 1110 patients) were included. Discrepancies were resolved by consensus agreement with a third reviewer. Clinical findings associated with the presence of hip OA included: a family history of OA (positive likelihood ratio [LR+] = 2.1; 1.2 - 3.6), a personal history of knee OA (LR+ = 2.1; 1.1 - 3.8), pain on climbing stairs or walking down slopes (LR+ = 2.1; 1.6 - 2.8), and the worst pain located in the medial thigh (LR+ = 7.8; 1.7 - 37). Findings associated with the absence of OA included: being younger than 60 years (negative likelihood ratio [LR-] = 0.11; 0.01 - 0.78), morning stiffness lasting less than 60 minutes (LR- range, 0.22 - 0.65), the absence of pain on walking (LR- range, 0.25 - 0.58), and the absence of pain improved by sitting (LR- = 0.24; 0.06 - 0.92). Physical findings associated with OA included: posterior hip pain caused by squatting (LR+ = 6.1; 1.3 - 29), groin pain on hip abduction or adduction (LR+ = 5.7; 1.6 - 20), abductor weakness (LR+ = 4.5; 2.4 - 8.4), decreased hip adduction (LR+ = 4.2; 3.0 - 6.0), and decreased internal rotation (LR+ = 3.2; 1.7 - 6.0). The absence of the following were useful in excluding OA: normal hip passive adduction (LR- = 0.25; 0.11 - 0.54) or abduction (LR- = 0.26; 0.09 - 0.77).
Bottom line: Although plain radiographs are often used to diagnosis hip osteoarthritis (OA), the correlation between radiographic indicators of hip arthritis and hip pain is low. Despite this, the accuracy of clinical symptoms and signs for diagnosing hip OA in this study is based on radiography as the gold standard. See the synopsis for a detailed list of accuracy findings.
Metcalfe D, Perry DC, Claireaux HA, Simel DL, Zogg CK, Costa ML. Does this patient have hip osteoarthritis? The rational clinical examination systematic review. JAMA 2019;322(23):2323-2333.

2. Usefulness of clinical tests for the diagnosis of infraspinatus tendon tears

Clinical question: What clinical signs and symptoms are useful for accurately diagnosing infraspinatus tendon tears in adults?
Study design: Diagnostic test evaluation **Setting:** Outpatient (specialty)
Synopsis: There are at least 6 established clinical tests for infraspinatus tendon tears: the Hornblower's sign, the drop sign, the Patte sign, the external rotation lag sign, the resisted external rotation test (RERT), and the infraspinatus scapular retraction test. These investigators identified 115 consecutive adults who presented with shoulder pain and were scheduled for shoulder arthroscopy. Of these, 91 who met inclusion criteria (no history of shoulder surgery and no evidence of shoulder instability, adhesive capsulitis, or calcific tendinitis) underwent examination by a single expert in sports medicine, followed by arthroscopy of the shoulder with specific examination of the articular and bursal side of the infraspinatus tendon. The initial examiner was unaware of the diagnosis for each individual patient and the surgeons performing the operations were masked to the results of the clinical tests. A total of 19 full thickness tears, 8 partial thickness tears, and 64 intact infraspinatus tendons were found at surgery. Only the drop sign (positive likelihood ratio [LR+] = 2.25; negative likelihood ratio [LR-] = 0.71) and the RERT (LR+ = 1.73; LR- = 0.34) as isolated tests accurately diagnosed the infraspinatus tendon tears, with muscle weakness instead of pain being considered when interpreting the RERT. The combination of the RERT and the Patte sign (LR+ = 1.29; LR- = 0.49) showed the highest correlation with intraoperative findings. None of the tests in isolation or combination accurately discriminated between partial thickness and full thickness tears. The authors describe the 3 useful tests as follows: (1) The drop sign: the arm is passively elevated to 90 degrees with the examiner supporting the elbow with one hand while rotating the arm to maximal external rotation with the other hand. The patient is asked to hold this position for 10 seconds. The result is considered positive if the arm drops back to internal rotation by more than 5 degrees; (2) The RERT: with the arm at zero degrees of abduction, the elbow at 90 degrees of flexion, and the shoulder at a neutral rotation, the patient is asked to externally rotate the arm against the examiner's resistance, with muscle weakness (not pain alone) considered a positive result; and (3) The Patte sign: with the arm at 90 degrees of elevation and 90 degrees of external rotation, and with the elbow at 90 degrees of flexion, the patients is asked to externally rotate the arm against the examiner's resistance. Either pain or weakness is considered a positive test result.
Bottom line: The most accurate single tests for diagnosing infraspinatus tendon tears in adults are the drop sign and the resisted external rotation test (RERT). The most accurate combination of tests includes the RERT and the Patte sign. No clinical tests in isolation or combination can accurately discriminate between partial thickness and full thickness tears.
Sgroi M, Loitsch T, Reichel H, Kappe T. Diagnostic value of clinical tests for infraspinatus tendon tears. Arthroscopy 2019;35(5):1339-1347.

3. Ultrasound is accurate for diagnosing upper extremity fractures in children

Clinical question: How accurate is ultrasound for diagnosing upper extremity fractures in children?

Study design: Meta-analysis (other) **Funding source:** Self-funded or unfunded **Setting:** Various (meta-analysis)
Synopsis: These authors searched PubMed, EMBASE, and the Web of Science to find studies that compared diagnostic ultrasound with an external reference standard to diagnose upper extremity fractures in children. The included studies used various reference standards: plain radiograph, magnetic resonance imaging, bone scan, and clinical diagnosis (you don't need an X-ray to know an arm bent to 90 degrees at midshaft is fractured). Two of the authors independently evaluated articles for inclusion and assessed the methodologic quality of the included studies. They resolved discrepancies through consensus, and through third-party adjudication if consensus could not be reached. They wound up with 32 studies with 2994 children; 27 were prospective studies. Seven studies used radiology-based ultrasound and 17 used point-of-care ultrasound. Nineteen studies took place in the emergency department. Overall, the studies were of mixed quality. Several studies didn't describe the setting, the training of those performing the ultrasound, or even the ages of the participants. Overall, ultrasound was 98% accurate based on the area under ROC curve. The sensitivity and specificity were high (0.95 for each); the positive likelihood ratio (LR+) was 21.1 (95% CI 10.8 - 41.5) and the negative likelihood ratio (LR-) was 0.05 (0.03 - 0.07). So, ultrasound was very good at both ruling in and ruling out fractures. However, when the authors looked at elbow fractures, ultrasound was 96% accurate with high sensitivity (0.95) but slightly lower specificity (0.87). For fractures involving the elbow, ultrasound was less accurate at ruling in fractures (LR+ 7.3; 3.7 - 14.4), but was still accurate at ruling them out (LR- 0.06; 0.02 - 0.16). The authors report high levels of heterogeneity in the data.
Bottom line: Diagnostic ultrasound is very accurate for diagnosing most upper extremity fractures, but slightly less accurate for fractures involving the elbow. Clinicians should not use ultrasound alone to rule in elbow fractures in children.
Tsou PY, Ma YK, Wang YH, Gillon JT, Rafael J, Deanehan JK. Diagnostic accuracy of ultrasound for upper extremity fractures in children: A systematic review and meta-analysis. Am J Emerg Med 2021;44:383-394.

Pain Management

In general, simple measures and placebo are effective approaches to managing musculoskeletal pain. The recurring theme the last few years has been that opioids are not much more effective than other measures.

4. Guideline: Topical NSAIDs should be first-line treatment for muscle pain

Clinical question: For musculoskeletal pain other than low back pain, what treatments are most likely to result in benefit?
Study design: Practice guideline **Setting:** Various (guideline)
Synopsis: These guidelines from the US internal medicine and family physician societies started with a meta-analysis of studies that evaluated treatments for musculoskeletal pain other than in the low back. The writers evaluated patient-oriented outcomes: pain, function, satisfaction with care, and cost. The guideline panel included 2 members of the public. They used a network meta-analysis to compare options not directly studied with one another, which is good but not great. None of the authors had a financial conflict of interest. Evidence was evaluated using the standard GRADE methodology. A recommendation was labeled "strong" if it applies to most patients because the evidence was clear that benefits outweighed harms; "conditional" if it applies to most patients, but there is uncertainty in the evidence, and patients' values and preferences should be more strongly considered. Based on moderate-certainty evidence, the groups strongly recommend initial treatment with a topical NSAID (only diclofenac is commercially available) because of demonstrated benefit on pain, function, and satisfaction with a low risk of side effects and a low cost. Given a moderate certainty of benefit and a moderate certainty of adverse effects, treatment with an oral NSAID is given a conditional recommendation. Acupressure and transcutaneous electrical nerve stimulation may also be offered, though the certainty of evidence is low. Given low-certainty evidence, the group recommends against opioids for treatment (conditional recommendation).
Bottom line: In a nod to the liniments of old, this guideline recommends topical nonsteroidal anti-inflammatory drugs (NSAIDs) with or without medicinal-smelling menthol gel as first-line treatment of musculoskeletal pain to reduce pain, improve function, and improve treatment satisfaction (strong recommendation). An oral NSAID, acetaminophen, or acupressure or transcutaneous electrical nerve stimulation can also be considered (conditional recommendation). The guideline advises against using opioids, including tramadol (Ultram, ConZip), for treatment.
Qaseem A, McLean RM, O'Gurek D, Batur P, Lin K, Kansagara DL. Nonpharmacologic and pharmacologic management of acute pain from non–low back, musculoskeletal injuries in adults: a clinical guideline from the American College of Physicians and American Academy of Family Physicians. Ann Intern Med 2020;173(9):739-748.

5. Short-term low back pain relief with placebo

Clinical question: Is placebo effective in patients with low back pain?
Study design: Randomized controlled trial (nonblinded) **Setting:** Outpatient (specialty)
Synopsis: These authors enrolled 127 patients with long-term low back pain – more than 70% of enrollees reported having back pain for more than 5 years. The average age was approximately 59 years and 60% were women. Initial pain scores were approximately 5 out of a possible 10 and roughly 20% of the patients were treated with analgesics at the time of enrollment. The patients were told, before enrollment, that the study would involve placebo treatment and were shown a video on the beneficial effects of placebo. They were then randomized, with allocation assignment unconcealed, to receive existing care or existing care plus placebo (Zeebo) to be taken twice daily for 21 days. The patients were told it was placebo. At the end of the study, a composite pain intensity score—comprising minimum, maximum, and average pain intensities during the last 7 days on an 11-point scale—dropped more with placebo treatment than with existing care alone (0.62 vs 0.11; P = .001), and subjective disability scores improved to a greater extent with placebo (3.21 decrease vs 0.65 increase; P = .02). Objective mobility or anxiety and stress scores were not affected. I wish the researchers would have masked the enrolling investigator to the treatment assignment at the time of enrollment (concealed allocation); randomization produced an imbalance in body mass index between the groups, which might have been due to chance or to selective enrollment of patients.

Bottom line: Over 3 weeks, patients with long-term low back pain who knowingly took placebo twice a day reported less pain and disability than those continuing with treatment as usual. This is not the only study to show the benefit of placebo. Whether the benefit persists is not known. A nonprescription product (Zeebo) is available, or pharmacists can prepare placebo capsules.
Kleine-Borgmann J, Schmidt K, Hellmann A, Bingel U. Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: a randomized controlled trial. Pain 2019;160(12):2891–2897.

6. Open-label placebo decreases opioid use after surgery

Clinical question: Can the addition of an open-label placebo decrease the need for opioid analgesia following surgery?
Study design: Randomized controlled trial (nonblinded) **Funding source:** Foundation **Setting:** Inpatient (ward only)
Synopsis: These researchers enrolled 51 patients undergoing spine surgery. In the recruiting process, potential participants were told about the nature of the study, the available research about the benefit of placebo treatment, and the idea that pairing placebo treatment with opioid analgesia might result in a conditioned response to the placebo (similar to the bell in Pavlov's experiments). The participants also underwent testing for pain levels, threshold, and tolerance before surgery. They were randomized, using concealed allocation, to receive standard postoperative analgesia treatment (oral treatment with acetaminophen and oxycodone or hydromorphone) or placebo combined with oral analgesia. The combined placebo/analgesia group was instructed to take a placebo with every analgesic dose for the first day, then to begin taking 3 daily scheduled placebo pills in addition to the placebo/analgesic combination, which should be taken according to pain relief needs. The thrice-daily placebo and as-needed combination placebo/analgesia were continued until the follow-up appointment. Patients in the placebo/analgesia group had approximately 30% less daily opioid use, an average –14.5 daily morphine milligram equivalents, compared with patients in the analgesia-only group over 17 days of follow-up. Daily worst pain scores were also lower in the placebo/analgesia group (–1.0 point on the 10-point scale; 95% CI –2.0 to –0.1), though average daily pain scores did not differ. This was a small study with quite a bit of attention paid to developing the conditioning response; it may be more difficult to implement in other settings.
Bottom line: I continue to be fascinated by the effectiveness of open-label placebo treatment; that is, the use of a treatment the patient *knows* is a placebo. Deliberate conditioning of patients to associate placebo with pain relief by initially combining it with analgesia dosing resulted in a 30% reduction in postoperative opioid analgesia use over the subsequent 17 days. Although not studied in outpatient management of pain, this type of deliberate conditioning to associate placebo with pain relief might be a new way to reduce opioid use for pain control.
Flowers KM, Patton ME, Hruschak VJ, et al. Conditioned open-label placebo for opioid reduction after spine surgery: a randomized controlled trial. Pain 2021;162(6):1828-1839.

7. Single-dose opioid analgesics offer no benefit over non-narcotic analgesia for musculoskeletal pain

Clinical question: For acute muscle pain, what oral analgesic provides the best immediate relief?
Study design: Randomized controlled trial (double-blinded) **Setting:** Emergency department
Synopsis: These researchers enrolled 600 adults, primarily Latinx, presenting to 2 emergency departments with a sprain, strain, fracture, or other musculoskeletal extremity pain. In other words, no back pain. The patients were randomly assigned, using concealed allocation, to receive a single dose of 1 of the 5 combinations of analgesics: 1000 mg acetaminophen with either 400 mg or 800 mg of ibuprofen, acetaminophen 300 mg with codeine 30 mg (Tylenol #3), acetaminophen 300 mg with hydrocodone 5 mg (Vicodin), or acetaminophen 325 mg with oxycodone 5 mg (Percocet). Pain scores before treatment were mostly 8 to 10 on a scale of 0 to 10 (with 10 being the worst pain). Pain scores dropped an average of 3 points in every group by 60 minutes after the medication dose, with no statistical difference among the groups. By 2 hours, the decrease from baseline was an average 4.3 to 4.7 points, with no significant differences among the groups. A similar percent of patients in each group (~ 24%) received rescue pain medication within the first 2 hours. The likelihood of nausea or vomiting was significantly higher among patients who received an opioid analgesic, with one additional patient experiencing these side effects for every 25 patients treated with an opioid (number needed to treat = 20; 95% CI 12 - 59). The study had the power to detect a difference of 1.3 points between treatments, if one existed.
Bottom line: A single dose of opioid analgesics provides similar acute pain relief to a single dose of a combination of acetaminophen and ibuprofen in patients with acute musculoskeletal pain in the emergency department. Opioids increase the likelihood of nausea or vomiting. There was no added benefit of 800 mg of ibuprofen as compared with 400 mg. Unfortunately, the study did not investigate the further effect, possibly because of the placebo effect, of an injectable analgesic. These results are similar to those of previous studies of opioids and different doses of ibuprofen.
Bijur PE, Friedman BW, Irizarry E, Chang AK, Gallagher EJ. A randomized trial comparing the efficacy of five oral analgesics for treatment of acute musculoskeletal extremity pain in the emergency department. Ann Emerg Med 2021;77(3):345-356.

Stop injecting (expensive) crap into tendons and joints

Corticosteroid injections provide short term but not long term relief for several musculoskeletal problems, multiple injections don't appear to provide much benefit.

8. MA: intra-articular corticosteroids provide short-term relief in patients with adhesive capsulitis

Clinical question: Which treatments for patients with adhesive capsulitis are effective?
Study design: Meta-analysis (randomized controlled trials) **Setting:** Various (meta-analysis)
Synopsis: These authors searched several databases and clinical trials registries to identify randomized trials of interventions to treat patients with adhesive capsulitis. The potential treatments included a whole boatload of stuff, including corticosteroids, sodium hyaluronate, platelet-rich plasma, nonsteroidal anti-inflammatory medications, collagenase Clostridium histolyticum, adalimumab, and saline; all delivered by mouth, by injection, or transdermally. Two authors independently assessed the studies for inclusion and for their methodologic quality. In addition to a traditional meta-analysis, the authors also performed a network meta-analysis to potentially

identify the most effective interventions. Ultimately, they identified 30 studies with 2132 patients. One study was published in 1954, the remainder were published after 1991. Only 6 of the trials was at low risk of bias and 23 were of unclear risk. The mean age of the patients ranged from 50 years to 65.8 years and all patients had symptoms for at least 3 weeks. Although the authors tried to identify all relevant studies, they reported finding statistical evidence of publication bias. Ultimately, after performing a bunch of statistical gymnastics, the authors found that various approaches to intra-articular steroid injections provided short-term clinically important improvements in pain, but no long-term benefits.
Bottom line: In this network meta-analysis, intra-articular steroid injections provide short-term clinically important improvements in pain, but no long-term benefits.
Kitridis D, Tsikopoulos K, Bisbinas I, Papaioannidou P, Givissis P. Efficacy of pharmacological therapies for adhesive capsulitis of the shoulder: A systematic review and network meta-analysis. Am J Sports Med 2019;47(14):3552-3560.

9. Ultrasound-guided steroid injections are more accurate than blind injections for frozen shoulder, but outcomes are similar

Clinical question: Are ultrasound-guided intra-articular steroid injections more accurate than blind injections?
Study design: Randomized controlled trial (single-blinded) **Funding source:** Government
Synopsis: These authors, at a single center in South Korea, enrolled patients with primary frozen shoulders (i.e., limited range of motion in at least 2 planes). They performed imaging to rule out other causes of the frozen shoulder and then randomized the patients to receive US-guided glenohumeral corticosteroid injections (n = 45) or blind injections (n = 45). A single experienced clinician performed all the injections from a posterior approach and used 40 mg triamcinolone acetonide, 4 mL 1% lidocaine, and 4 mL normal saline. Additionally, 3 mL water-soluble contrast was injected to allow for post-injection fluoroscopy confirmation of the injection location. The researcher placed the US transducer just under the acromion for each patient, but the imagers was not turned on for those randomized to receive blind injections. Other than a difference in which side was affected, the 2 groups were similar at baseline. All patients were told to perform frozen shoulder exercises (e.g., pendulum, wall-climbing, etc.) at home. Based on the fluoroscopy, evaluated without awareness of which approach was used, 100% of the US-guided injections hit the mark compared with 71% of the blind injections. However, at 3 weeks, 6 weeks, and 12 weeks, patients in each group had clinically meaningful improvements in pain on a visual analog scale and the degree of improvement was comparable between the 2 groups. Similarly, the researchers found similar degrees of improvements in several other measures of mobility and function. When the authors analyzed the outcomes based on whether the injection hit the mark, they also found no differences between the 2 groups on their various measures. Finally, they report that no patient in either group experienced any adverse events: infection, necrosis, vasovagal syncope, systemic anesthetic toxicity, or contrast medium anaphylaxis.
Bottom line: In this study from at a single center where steroid injections were given by a single experienced clinician, ultrasound (US)-guided intra-articular injections were more accurate than blind injection. But the outcomes, even among those that "missed," were similar.
Cho CH, Min BW, Bae KC, Lee KJ, Kim DH. A prospective double-blind randomized trial on ultrasound-guided versus blind intra-articular corticosteroid injections for primary frozen shoulder. Bone Joint J 2021;103-B(2):353-359.

10. Multiple steroid injections into arthritic joints do not improve outcomes more than other injections

Clinical question: Are multiple intra-articular corticosteroid injections more effective and safer than other joint injections in patients with degenerative joint disease?
Study design: Meta-analysis (randomized controlled trials) **Setting:** Various (meta-analysis)
Synopsis: These authors searched several databases to identify randomized controlled trials (RCTs) and observational studies that evaluated multiple corticosteroid injections into the joints of patients with radiographically confirmed degenerative joint disease. The comparator could be placebo, saline, or another active agent like hyaluronic acid. The authors used the RCTs to evaluate pain response and both the RCTs and observational studies to evaluate harms. They evaluated the risk of bias for the RCTs but not the observational studies. For efficacy, they identified 6 small trials (666 patients); their search for safety data identified 14 RCTs and 2 observational studies. The RCTs were diverse: 4 trials included patients with knee degenerative joint disease, 1 trial looked at temporomandibular joints, and 1 trial looked at the first carpometacarpal joint. Three trials were of injected betamethasone, 2 were of injected triamcinolone, and 1 was of injected methylprednisolone; the number of injections ranged from 2 to 8. Four studies compared steroids with hyaluronic acid; 2 studies used saline as the comparator. Overall, the reporting of the individual trials was spotty, making their overall risk of bias unclear. This is not a good sign. Despite all the messiness, the authors chose to pool the data and report that, overall, patients who received multiple steroid injections had an approximately 0.5 standardized mean difference in pain improvement over the patients who received a comparator. Although this is statistically significant, it is unlikely to be clinically important. The authors did some subgroup analyses but given the small number of studies and the aforementioned messiness, these were all pretty meaningless. Other than minor local phenomena, adverse events were rare and none of the studies reported an instance of a septic joint. Only one study reported a single participant who developed malaise, tachycardia, and hypotension after the first injection and had to withdraw from the study. Two studies reported greater cartilage loss and greater joint space narrowing in the steroid-injected patients. One cohort study found that patients who received multiple steroid injections were also more likely to undergo joint replacement, although this is as likely to represent confounding by indication as a harm of treatment. Finally, lumping together non–weight-bearing joints and weight-bearing joints as if they respond to treatment similarly potentially misses important effects for specific joints.
Bottom line: In this systematic review, patients with degenerative joint disease who received multiple corticosteroid injections did not have more meaningful pain relief than those who received other injections. Since 2 studies reported either cartilage loss or joint space narrowing among steroid-treated patients, more data are needed to determine just how safe they are.
Ayub S, Kaur J, Hui M, et al. Efficacy and safety of multiple intra-articular corticosteroid injections for osteoarthritis—a systematic review and meta-analysis of randomized controlled trials and observational studies. Rheumatology (Oxford) 2021;60(4):1629-1639.

In the past few years randomized trials, contrary to “expert opinion” or “expert experience,” have found that injecting crap (stem cells, ozone, platelet-rich plasma, prolotherapy, etc.) other than corticosteroids into joints is no more effective than placebo. These are often expensive and not covered by insurance. Here are a couple of studies that illustrate this.

11. Platelet-rich plasma injection is no better than sham injection for midportion Achilles’ tendinopathy

Clinical question: Is an injection of platelet-rich plasma effective in reducing pain and improving function in adults with chronic midportion Achilles tendinopathy?
Study design: Randomized controlled trial (single-blinded) **Funding source:** Foundation **Setting:** Outpatient (specialty)
Synopsis: Platelet-rich plasma (PRP) injections are pathophysiologically linked to promoting tendon repair by concentrating growth factor at the site of chronic degeneration. These investigators identified 240 adults, 18 years or older, with pain at the midportion of the Achilles tendon for at least 3 months and tendinopathy confirmed by ultrasound, magnetic resonance imaging, or both. Eligible patients randomly received (concealed allocation assignment) a PRP injection by palpation (i.e., not guided by ultrasound) of leukocyte-rich material prepared from whole-blood centrifugation or sham injection (dry injection inserted under the skin overlying the tendon). Both syringes were masked with black tape. Patients unaware of group assignment self-assessed their outcomes using a validated scoring tool for Achilles tendinopathy. Complete follow-up occurred for 92% of participants at 6 months.
Using intention-to-treat analysis, no significant group differences occurred in pain, function, or activity level. The study was 90% powered to detect a pre-determined clinically significant between-groups difference in pain and function scores.
Bottom line: This study found no additional benefit to a PRP injection compared with sham injection in reducing pain or improving function in adults with chronic midportion Achilles tendinopathy.
Kearney RS, Ji C, Warwick J, et al, for the ATM Trial Collaborators. Effect of platelet-rich plasma injection vs sham injection on tendon dysfunction in patients with chronic midportion Achilles tendinopathy: a randomized clinical trial. JAMA 2021;326(2):137-144.

12. Platelet-rich plasma = saline for patients with patellar tendinopathy

Clinical question: Are platelet-rich plasma injections effective in patients with patellar tendinopathy?
Study design: Randomized controlled trial (single-blinded) **Setting:** Outpatient (specialty)
Synopsis: In this multicenter (Seattle, Oslo, Bologna) trial, the authors enrolled 61 adults, 18 years to 50 years of age, with at least 6 months of clinically diagnosed patellar tendinopathy confirmed by ultrasound with persistent symptoms in spite of a minimum of 6 weeks of exercise-based rehabilitation. The authors randomized patients to receive ultrasound-guided injections of either leukocyte-rich platelet-rich plasma, leukocyte-poor platelet-rich plasma, or saline. One week later, all patients engaged in a supervised gym-based rehabilitation program 3 times weekly for 6 weeks. Using standardized scales, the researchers evaluated each patient's pain, function, and activity limitations at baseline, and at 12, 24, and 52 weeks after the injections. Additionally, they asked the patients' for their own overall rating of change at the subsequent assessments. They had nearly complete (93%) follow-up at 12 weeks, but only 79% at the end of a year. At no point in the study did the authors find any differences in the 3 groups as to any of the outcomes or patient global assessment of improvement. Six weeks after the intervention, 5 patients, none whom received saline, reported overall worsening compared with their baseline. The authors report one patient experienced localized patellar tendon pain following the injection, enough to prevent activity. No other harms are reported, possibly because of the small sample size. The study was large enough to detect clinically meaningful differences in pain and functional limitations.
Bottom line: In this study, platelet-rich plasma injections were no better than saline injections in improving pain or activity in patients with patellar tendinopathy. It did not matter if the plasma was leukocyte rich or leukocyte poor. The study was too small to detect potential harms of the intervention.
Scott A, LaPrade RF, Harmon KG, et al. Platelet-rich plasma for patellar tendinopathy: a randomized controlled trial of leukocyte-rich PRP or leukocyte-poor PRP versus saline. Am J Sports Med 2019;47(7):1654-1661.

13. RESTORE Trial: PRPP=placebo for pain relief and improving structure in persons with knee DJD

Importance: Most clinical guidelines do not recommend platelet-rich plasma (PRP) for knee osteoarthritis (OA) because of lack of high-quality evidence on efficacy for symptoms and joint structure, but the guidelines emphasize the need for rigorous studies. Despite this, use of PRP in knee OA is increasing. **Objective:** To evaluate the effects of intra-articular PRP injections on symptoms and joint structure in patients with symptomatic mild to moderate radiographic medial knee OA. **Design, Setting, and Participants:** This randomized, 2-group, placebo-controlled, participant-, injector-, and assessor-blinded clinical trial enrolled community-based participants (n = 288) aged 50 years or older with symptomatic medial knee OA (Kellgren and Lawrence grade 2 or 3) in Sydney and Melbourne, Australia, from August 24, 2017, to July 5, 2019. The 12-month follow-up was completed on July 22, 2020. **Interventions:** Interventions involved 3 intra-articular injections at weekly intervals of either leukocyte-poor PRP using a commercially available product (n = 144 participants) or saline placebo (n = 144 participants). **Main Outcomes and Measures:** The 2 primary outcomes were 12-month change in overall average knee pain scores (11-point scale; range, 0-10, with higher scores indicating worse pain; minimum clinically important difference of 1.8) and percentage change in medial tibial cartilage volume as assessed by magnetic resonance imaging (MRI). Thirty-one secondary outcomes (25 symptom related and 6 MRI assessed; minimum clinically important difference not known) evaluated pain, function, quality of life, global change, and joint structures at 2-month and/or 12-month follow-up. **Results:** Among 288 patients who were randomized (mean age, 61.9 [SD, 6.5] years; 169 [59%] women), 269 (93%) completed the trial. In both groups, 140 participants (97%) received all 3 injections. After 12 months, treatment with PRP vs placebo injection resulted in a mean change in knee pain scores of -2.1 vs -1.8 points, respectively (difference, -0.4 [95% CI, -0.9 to 0.2] points; P = .17). The mean change in medial tibial cartilage volume was -1.4% vs -1.2%, respectively (difference, -0.2% [95% CI, -1.9% to 1.5%]; P = .81). Of 31 prespecified secondary outcomes, 29 showed no significant between-group differences. **Conclusions and Relevance:** Among patients with symptomatic mild to moderate radiographic knee OA, intra-articular injection of PRP, compared with injection of saline placebo, did

not result in a significant difference in symptoms or joint structure at 12 months. These findings do not support use of PRP for the management of knee OA.
Bennell KL, Paterson KL, Metcalf BR, et al. Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. JAMA. 2021;326(20):2021-2030.

Special footwear for persons with knee DJD

The data on the effectiveness of footwear from the last few years are mixed as is seen in the next two studies.

14. Type of shoe doesn't seem to matter for moderate to severe knee osteoarthritis due to medial joint space narrowing

Clinical question: Are flat flexible shoes as effective as stable supportive shoes to decrease pain in patients with knee osteoarthritis?
Study design: Randomized controlled trial (single-blinded) **Setting:** Emergency department
Synopsis: These researchers recruited patients with knee pain and moderate to severe osteoarthritis with primarily medial joint space narrowing. Most (81%) were taking an analgesic. The 164 patients were given, using concealed allocation, 2 pairs of a particular type of shoe to be worn exclusively for 6 months (since shoes can reduce medial knee loading). The shoes were either flat and flexible (think minimalist shoes, such as Vivobarefoot or Merrell Bare Access) or stable and supportive (such as Rockport Edge Hill or a stability walking shoe). The patients got to pick the color. Almost all patients (98%) completed the study. The stable supportive shoes were slightly better at reducing knee pain (1.1 units on an 11-point scale; P = .001), but this difference is not likely to be clinically relevant. Function improved similarly in both groups. Knee-related quality of life and hip pain were slightly better with supportive shoes. Adverse effects — self-identified problems in the study knee or elsewhere in the body attributed to the shoes — were twice as high with flexible shoes (32% vs 15%).
Bottom line: Tell patients with knee pain to experiment to see if changing their shoe type produces pain relief. In this study, supportive shoes produce a little more pain relief in patients with moderate to severe osteoarthritis than minimalist flat and flexible shoes, but the difference is not likely clinically relevant. Function, knee-related quality of life, and hip pain are not significantly better, on average, with one type of shoe over another, though patients in each group responded to their new shoes.
Paterson KL, Bennell KL, Campbell PK, et al. The effect of flat flexible versus stable supportive shoes on knee osteoarthritis symptoms: a randomized trial. Ann Intern Med 2021;174(4):462–471.

15. Biomechanical footwear may be effective for reducing pain in adults with knee DJD

Clinical question: Is individually calibrated biomechanical footwear therapy effective for reducing pain and improving function in adults with knee degenerative joint disease?
Study design: Randomized controlled trial (single-blinded) **Setting:** Outpatient (any)
Synopsis: A biomechanical footwear system consists of shoes with 2 convex pods on the outsoles, which can be individually calibrated to alter limb biomechanics and reduce stress on osteoarthritic knees. These investigators identified adults (N = 220), 40 years or older, with symptomatic radiologically confirmed knee DJD lasting at least 6 months. Eligible participants randomly received (via concealed assignment) either the biomechanical footwear or control footwear specifically designed to have a similar appearance but no capacity to be individually calibrated. Patients masked to their treatment group assignment self-assessed outcomes using validated pain, function, and quality-of-life scoring tools. Complete follow-up occurred for 96.8% of patients at 24 weeks. Using intention-to-treat analysis, the mean pain score improved from 4.3 at baseline to 1.3 in the biomechanical footwear group and from 4.0 to 2.6 in the control group (between-group difference, -1.3; 95% CI -1.8 to -0.9; range 0–10, where 0 = no symptoms and 10 = extreme symptoms). Significantly more patients in the biomechanical footwear group achieved a 50% reduction in pain scores compared with patients in the control footwear group (83% vs 42%; number needed to treat = 3; 1 - 4). Similar results occurred for function scores, but there were no significant between-group differences for overall quality-of-life improvement. Similarly, the rate of rescue analgesic use did not differ between groups.
Bottom line: In adults with symptomatic knee degenerative joint disease (DJD), the use of biomechanical footwear statistically significantly reduced pain compared with control footwear. The overall mean pain reduction score was approximately 1 on a visual analog scale of 0–10 (a difference of 2 or more is generally considered clinically significant). No between-group differences occurred in overall quality-of-life scores.
Reichenbach, S, Felson DT, Hincapie CA, et al. Effect of biomechanical footwear on knee pain in people with knee osteoarthritis. The BIOTOK randomized clinical trial. JAMA 2020;323(18):1802-1812.

Injuries

16. Long-term outcomes are similar with below- and above-elbow casts in children with minimally displaced forearm fractures

Clinical question: In children with minimally displaced forearm fractures, are long-term outcomes similar with below-elbow casts and above-elbow casts?
Study design: Randomized controlled trial (nonblinded) **Setting:** Outpatient (specialty)
Synopsis: This is a follow-up of a trial in which children with a minimally displaced fracture of the metaphysis of both the radius and ulna were randomized to 4 weeks of treatment with a below-elbow cast (n = 35) or an above-elbow cast (n = 31). Of the original 66 children, the authors had a median of 7.3 years of follow-up on 51 kids. Those treated with below-elbow casts and above-elbow casts

showed no significant differences in loss of forearm rotation or angulation. More important, there was also no difference in strength, function, or cosmetic appearance.
Bottom line: In this small study, the long-term cosmetic and functional outcomes of children with minimally displaced forearm fractures treated with below-elbow casts and above-elbow casts are similar.
Musters L, Diederix LW, Roth KC, et al. Below-elbow cast sufficient for treatment of minimally displaced metaphyseal both-bone fractures of the distal forearm in children: long-term results of a randomized controlled multicenter trial. Acta Orthop 2021;92(4):468-471.

17. Vitamin D supplementation *increases* risk of fall-related fractures in the elderly

BACKGROUND/OBJECTIVES: To assess whether vitamin D supplementation prevents specific fall subtypes and sequelae (e.g., fracture). **DESIGN:** Secondary analyses of STURDY (Study to Understand Fall Reduction and Vitamin D in You)-a response-adaptive, randomized clinical trial. **SETTING:** Two community-based research units. **PARTICIPANTS:** Six hundred and eighty-eight participants >/=70 years old with elevated fall risk and baseline serum 25-hydroxyvitamin D levels of 10-29 ng/ml. **INTERVENTION:** 200 IU/day (control), 1000 IU/day, 2000 IU/day, or 4000 IU/day of vitamin D3. **MEASUREMENTS:** Outcomes included repeat falls and falls that were consequential, were injurious, resulted in emergency care, resulted in fracture, and occurred either indoors or outdoors. **RESULTS:** After adjustment for multiple comparisons, the risk of fall-related fracture was greater in the pooled higher doses (>/=1000 IU/day) group compared with the control (hazard ratio [HR] = 2.66; 95% confidence interval [CI]:1.18-6.00). Although not statistically significant after multiple comparisons adjustment, time to first outdoor fall appeared to differ between the four dose groups (unadjusted p for overall difference = 0.013; adjusted p = 0.222), with risk of a first-time outdoor fall 39% lower in the 1000 IU/day group (HR = 0.61; 95% CI: 0.38-0.97; unadjusted p = 0.036; adjusted p = 0.222) and 40% lower in the 2000 IU/day group (HR = 0.60; 95%CI 0.38-0.97; p = 0.037; adjusted p = 0.222), each versus control. **CONCLUSION:** Vitamin D supplementation doses >/=1000 IU/day might have differential effects on fall risk based on fall location and fracture risk, with the most robust finding that vitamin D doses between 1000 and 4000 IU/day might increase the risk of first time falls with fractures. Replication is warranted, given the possibility of type 1 error.
Wanigatunga AA, Sternberg AL, Blackford AL, et al. The effects of vitamin D supplementation on types of falls. J Am Geriatr Soc. 2021;69(10):2851-2864.

Bottom Lines:

- Diagnostic ultrasound is accurate in diagnosing
- Use topical NSAIDs as first line treatment of musculoskeletal pain
- Platelet-rich plasma injections are ineffective.
- Below elbow casts are as effective as above elbow casts in children with uncomplicated fractures of the metaphysis of the radius and ulna

Endocrine Update — Gary Ferenchick MD

Learning objectives | Understand and apply:

- Diagnosing and treating subclinical hypothyroidism (SCH) is not associated with clinical benefit for most adults
- Hyperaldosteronism is common, but not commonly diagnosed
- Male hypogonadism is associated with sexual dysfunction; & testosterone replacement is associated with improved sexual function

Sub clinical hypothyroidism (SCH)

Definition

- The definition of SCH varies. About 90% of all patients with SCH have TSH levels between 4 and 10 mIU/L. TSH levels may increase with age, and a slight increase of TSH may be normal for older people.
- There is biological variation in TSH levels.
- Levels may rise in response to stress and transient disease.
- This biological variation in TSH values, means that one abnormal TSH level should be followed by a repeat blood test to confirm the diagnosis.
- About 62% of TSH levels 4 to 10 mIU/L normalize without intervention within 5 years.

How common is SCH?

- It affects 4-20% of the adult population.
- This wide variation is due to poor consensus about the cut-off level for the diagnosis of SCH and regional variation between populations.
- It is more common in women, in older people, and those of white ethnicity.

What are the symptoms?

- Around 1 in 3 patients with SCH have no symptoms at all.
- The type of symptoms people link to SCH include those of overt hypothyroidism:
    - Fatigue
    - Muscle cramps
    - Cold sensitivity
    - Dry skin
    - Voice changes
    - Constipation
    - Other symptoms include:
    - Poor memory
    - Slowed thinking
    - weak muscles
    - puffy eyes
    - anxiety
    - depression
- Many of these symptoms are not specific to hypothyroidism.
- Around 20-25% of people with normal TSH levels report one or two of these symptoms.
- The relation between symptoms and biochemical TSH levels remains unclear.

What is the long-term outlook?

- The risk of progression to overt hypothyroidism ranges between 2% and 5% a year.
- Presence of antibodies to thyroid peroxidase and, in particular, higher TSH levels increase this risk.

- Observational data suggest that SCH is associated with an increased risk of coronary heart disease, heart failure, and cardiovascular mortality, particularly in those with TSH levels >10 mIU/L.
- Such associations were not found for most adults with TSH levels of 5-10 mIU/L.

USPSTF 2021		
Population	**Recommendation**	**Grade**
Nonpregnant, asymptomatic adults	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.	I

Table 1 | Current guidance on thyroid hormone treatment for subclinical hypothyroidism

Organisation	Recommendation
National Institute for Health and Care Excellence (NICE) CKS guidelines, 2018[21]	• TSH >10 mIU/L: - Age <70 years, treat - Age ≥70 years, watch and wait • TSH 4-10 mIU/L: - Age <65 years with symptoms, consider trial - Age ≥65 years, watch and wait
European Thyroid Association (ETA), 2013[5]	• Age <70 years: - TSH >10 mIU/L, treat - TSH <10 mIU/L with symptoms, start trial - TSH <10 mIU/L without symptoms, observe • Age >70 years: - TSH <10 mIU/L, observe - TSH >10 mIU/L, consider treatment if clear symptoms or high cardiovascular risk
American Thyroid Association (ATA), 2012[8]	• TSH >10 mIU/L, consider treatment • TSH <10 mIU/L, consider treatment if symptoms suggestive of hypothyroidism, positive antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or risk factors for these diseases
UpToDate, 2018[22]	• TSH <7 mIU/L: - Age >65/70 years, observe - Age <65/70 years, treat if symptoms, observe without symptoms • TSH 7-10 mIU/L: - Age >65/70 years, treat if symptoms, observe without symptoms - Age <65 years, treat • TSH >10 mIU/L: treat

Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

#1: Reported # symptoms with SCH = Euthyroid

Background: Few studies have scrutinized the spectrum of symptoms in subclinical hypothyroidism.
Methods: From 3 Danish Investigation on Iodine Intake and Thyroid Diseases (DanThyr) cross-sectional surveys performed in the period 1997 to 2005, a total of 8903 subjects participated in a comprehensive investigation including blood samples and questionnaires on previous diseases, smoking habits, alcohol intake, and education. From the 3 surveys we included patients with subclinical hypothyroidism (n = 376) and euthyroid controls (n = 7619). We explored to what extent patients with subclinical hypothyroidism reported 13 previously identified hypothyroidism-associated symptoms (tiredness, dry skin, mood lability, constipation, palpitations, restlessness, shortness of breath, wheezing, globus sensation, difficulty swallowing, hair loss, dizziness/vertigo, and anterior neck pain). In various uni- and multivariate regression models we searched for circumstances predicting why some patients have more complaints than others.
Results: Subclinically hypothyroid patients did not report higher hypothyroidism score [(median, interquartile range), 2 (0-4) vs 2 (0-4), P = .25] compared with euthyroid controls. Within the group of subclinical hypothyroid patients, comorbidity had the highest impact on symptoms (tiredness, shortness of breath, wheezing; all P < .001); TSH level had no impact on symptom score; and younger age was accompanied by higher mental burden (tiredness, P < .001; mood lability, P < .001; restlessness, P = .012), whereas shortness of breath was associated with high body mass index (P < .001) and smoking (P = .007).
Conclusion: Patients with a thyroid function test suggesting subclinical hypothyroidism do not experience thyroid disease-related symptoms more often than euthyroid subjects. In subclinical hypothyroidism, clinicians should focus on concomitant diseases rather than expecting symptomatic relief following levothyroxine substitution.
Reference: Carlé A et al. Does Subclinical Hypothyroidism Add Any Symptoms? Evidence from a Danish Population-Based Study. Am J Med. 2021 Sep;134(9):1115-1126.e1.

#2: SCH not associated with cognitive function,

Importance: In clinical guidelines, overt and subclinical thyroid dysfunction are mentioned as causal and treatable factors for cognitive decline. However, the scientific literature on these associations shows inconsistent findings.
Objective: To assess cross-sectional and longitudinal associations of baseline thyroid dysfunction with cognitive function and dementia.
Design, setting, and participants: This multicohort individual participant data analysis assessed 114 267 person-years (median, 1.7-11.3 years) of follow-up for cognitive function and 525 222 person-years (median, 3.8-15.3 years) for dementia between 1989 and 2017. Analyses on cognitive function included 21 cohorts comprising 38 144 participants. Analyses on dementia included eight cohorts with a total of 2033 cases with dementia and 44 573 controls. Data analysis was performed from December 2016 to January 2021.
Exposures: Thyroid function was classified as overt hyperthyroidism, subclinical hyperthyroidism, euthyroidism, subclinical hypothyroidism, and overt hypothyroidism based on uniform thyrotropin cutoff values and study-specific free thyroxine values.
Main outcomes and measures: The primary outcome was global cognitive function, mostly measured using the Mini-Mental State Examination. Executive function, memory, and dementia were secondary outcomes. Analyses were first performed at study level using multivariable linear regression and multivariable Cox regression, respectively. The studies were combined with restricted maximum likelihood meta-analysis. To overcome the use of different scales, results were transformed to standardized mean differences. For incident dementia, hazard ratios were calculated.
Results: Among 74 565 total participants, 66 567 (89.3%) participants had normal thyroid function, 577 (0.8%) had overt hyperthyroidism, 2557 (3.4%) had subclinical hyperthyroidism, 4167 (5.6%) had subclinical hypothyroidism, and 697 (0.9%) had overt hypothyroidism. The study-specific median age at baseline varied from 57 to 93 years; 42 847 (57.5%) participants were women. Thyroid dysfunction was not associated with global cognitive function; the largest differences were observed between overt hypothyroidism and euthyroidism-cross-sectionally (-0.06 standardized mean difference in score; 95% CI, -0.20 to 0.08; P = .40) and longitudinally (0.11 standardized mean difference higher decline per year; 95% CI, -0.01 to 0.23; P = .09). No consistent associations were observed between thyroid dysfunction and executive function, memory, or risk of dementia.
Conclusions and relevance: In this individual participant data analysis of more than 74 000 adults, subclinical hypothyroidism and hyperthyroidism were not associated with cognitive function, cognitive decline, or incident dementia. No rigorous conclusions can be drawn regarding the role of overt thyroid dysfunction in risk of dementia. These findings do not support the practice of screening for subclinical thyroid dysfunction in the context of cognitive decline in older adults as recommended in current guidelines.
Reference: van Vliet NA et al. Association of Thyroid Dysfunction With Cognitive Function: An Individual Participant Data Analysis. JAMA Intern Med. 2021 Nov 1;181(11):1440-1450.

#3: Older patients with SCH, T4 provides no apparent benefits

BACKGROUND: The use of levothyroxine to treat subclinical hypothyroidism is controversial. We aimed to determine whether levothyroxine provided clinical benefits in older persons with this condition.
METHODS: We conducted a double-blind, randomized, placebo-controlled, parallel-group trial involving 737 adults who were at least 65 years of age and who had persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter; free thyroxine level within the reference range). A total of 368 patients were assigned to receive levothyroxine (at a starting dose of 50 μg daily, or 25 μg if the body weight was <50 kg or the patient had coronary heart disease), with dose adjustment according to the thyrotropin level; 369 patients were assigned to receive placebo with mock dose adjustment. The two primary outcomes were the change in the Hypothyroid Symptoms score and Tiredness score on a thyroid-related quality-of-life questionnaire at 1 year (range of each scale is 0 to 100, with higher scores indicating more symptoms or tiredness, respectively; minimum clinically important difference, 9 points).
RESULTS: The mean age of the patients was 74.4 years, and 396 patients (53.7%) were women. The mean (±SD) thyrotropin level was 6.40±2.01 mIU per liter at baseline; at 1 year, this level had decreased to 5.48 mIU per liter in the placebo group, as compared with 3.63 mIU per liter in the levothyroxine group (P<0.001), at a median dose of 50 μg. We found no differences in the mean change at 1 year in the Hypothyroid Symptoms score (0.2±15.3 in the placebo group and 0.2±14.4 in the levothyroxine group; between-group

difference, 0.0; 95% confidence interval [CI], –2.0 to 2.1) or the Tiredness score (3.2±17.7 and 3.8±18.4, respectively; between-group difference, 0.4; 95% CI, –2.1 to 2.9). No beneficial effects of levothyroxine were seen on secondary-outcome measures. There was no significant excess of serious adverse events prespecified as being of special interest.
CONCLUSIONS: Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism. (Funded by European Union FP7 and others; TRUST ClinicalTrials.gov number, NCT01660126.)
REFERENCE: Stott DJ et al.Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med 2017; 376:2534-2544

#4: Patients > 80 with SCH, T4 of no benefit for symptoms

Importance: It is unclear whether levothyroxine treatment provides clinically important benefits in adults aged 80 years and older with subclinical hypothyroidism.
Objective: To determine the association of levothyroxine treatment for subclinical hypothyroidism with thyroid-related quality of life in adults aged 80 years and older.
Design, setting, and participants: Prospectively planned combined analysis of data involving community-dwelling adults aged 80 years and older with subclinical hypothyroidism. Data from a randomized clinical trial were combined with a subgroup of participants aged 80 years and older from a second clinical trial. The trials were conducted between April 2013 and May 2018. Final follow-up was May 4, 2018.
Exposures: Participants were randomly assigned to receive levothyroxine (n = 112; 52 participants from the first trial and 60 from the second trial) or placebo (n = 139; 53 participants from the first trial and 86 from the second trial).
Main outcomes and measures: Co-primary outcomes were Thyroid-Related Quality of Life Patient-Reported Outcome (ThyPRO) questionnaire scores for the domains of hypothyroid symptoms and tiredness at 1 year (range, 0-100; higher scores indicate worse quality of life; minimal clinically important difference, 9).
Results: Of 251 participants (mean age, 85 years; 118 [47%] women), 105 were included from the first clinical trial and 146 were included from the second clinical trial. A total of 212 participants (84%) completed the study. The hypothyroid symptoms score decreased from 21.7 at baseline to 19.3 at 12 months in the levothyroxine group vs from 19.8 at baseline to 17.4 at 12 months in the placebo group (adjusted between-group difference, 1.3 [95% CI, -2.7 to 5.2]; P = .53). The tiredness score increased from 25.5 at baseline to 28.2 at 12 months in the levothyroxine group vs from 25.1 at baseline to 28.7 at 12 months in the placebo group (adjusted between-group difference, -0.1 [95% CI, -4.5 to 4.3]; P = .96). At least 1 adverse event occurred in 33 participants (29.5%) in the levothyroxine group (the most common adverse event was cerebrovascular accident, which occurred in 3 participants [2.2%]) and 40 participants (28.8%) in the placebo group (the most common adverse event was pneumonia, which occurred in 4 [3.6%] participants).
Conclusions and relevance: In this prospectively planned analysis of data from 2 clinical trials involving adults aged 80 years and older with subclinical hypothyroidism, treatment with levothyroxine, compared with placebo, was not significantly associated with improvement in hypothyroid symptoms or fatigue. These findings do not support routine use of levothyroxine for treatment of subclinical hypothyroidism in adults aged 80 years and older.
Reference: Mooijaart SP et al. Association Between Levothyroxine Treatment and Thyroid-Related Symptoms Among Adults Aged 80 Years and Older With Subclinical Hypothyroidism. JAMA. 2019 Nov 26;322(20):1977-1986.

#5: Pts with SCH, T4 provides no benefit

Importance: The benefit of thyroid hormone therapy for subclinical hypothyroidism is uncertain. New evidence from recent large randomized clinical trials warrants an update of previous meta-analyses.
Objective: To conduct a meta-analysis of the association of thyroid hormone therapy with quality of life and thyroid-related symptoms in adults with subclinical hypothyroidism.
Data Sources: PubMed, EMBASE, ClinicalTrials.gov, Web of Science, Cochrane Library, CENTRAL, Emcare, and Academic Search Premier from inception until July 4, 2018.
Study Selection: Randomized clinical trials that compared thyroid hormone therapy with placebo or no therapy in nonpregnant adults with subclinical hypothyroidism were eligible. Two reviewers independently evaluated eligibility based on titles and abstracts of all retrieved studies. Studies not excluded in this first step were independently assessed for inclusion after full-text evaluation by 2 reviewers.
Data Extraction and Synthesis: Two independent reviewers extracted data, assessed risk of bias (Cochrane risk-of-bias tool), and evaluated the quality of evidence (GRADE tool). For synthesis, differences in clinical scores were transformed (eg, quality of life) into standardized mean differences (SMDs; positive values indicate benefit of thyroid hormone therapy; 0.2, 0.5, and 0.8 correspond to small, moderate, and large effects, respectively). Random-effects models for meta-analyses were applied.
Main Outcomes and Measures: General quality of life and thyroid-related symptoms after a minimum follow-up of 3 months.
Results: Overall, 21 of 3088 initially identified publications met the inclusion criteria, with 2192 adults randomized. After treatment (range, 3-18 months), thyroid hormone therapy was associated with lowering the mean thyrotropin value into the normal reference range compared with placebo (range, 0.5-3.7 mIU/L vs 4.6 to 14.7 mIU/L) but was not associated with benefit regarding general quality of life (n = 796; SMD, −0.11; 95% CI, −0.25 to 0.03; I^2=66.7%) or thyroid-related symptoms (n = 858; SMD, 0.01; 95% CI, −0.12 to 0.14; I^2=0.0%). Overall, risk of bias was low and the quality of evidence assessed with the GRADE tool was judged moderate to high.
Conclusions and Relevance: Among nonpregnant adults with subclinical hypothyroidism, the use of thyroid hormone therapy was not associated with improvements in general quality of life or thyroid-related symptoms. These findings do not support the routine use of thyroid hormone therapy in adults with subclinical hypothyroidism.
Reference: Feller et al. Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism. A Systematic Review and Meta-analysis. JAMA. 2018;320(13):1349-1359.

#6: Depressive symptoms not affected by levothyroxine therapy

Importance: Previous trials on the effect of levothyroxine on depressive symptom scores in patients with subclinical hypothyroidism were limited by small sample sizes (N = 57 to 94) and potential biases.
Objective: To assess the effect of levothyroxine on the development of depressive symptoms in older adults with subclinical hypothyroidism in the largest trial on this subject and to update a previous meta-analysis including the results from this study.
Design, setting, and participants: This predefined ancillary study analyzed data from participants in the Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism (TRUST) trial, a double-blind, randomized, placebo-controlled, parallel-group clinical trial conducted from April 2013 to October 31, 2016. The TRUST trial included adults aged 65 years or older diagnosed with subclinical hypothyroidism, defined as the presence of persistently elevated thyroid-stimulating hormone (TSH) levels (4.6-19.9 mIU/L) with free thyroxine (T4) within the reference range. Participants were identified from clinical and general practitioner laboratory databases and recruited from the community in Switzerland, the Netherlands, Ireland, and the UK. This ancillary study included a subgroup of 472 participants from the Netherlands and Switzerland; after exclusions, a total of 427 participants (211 randomized to levothyroxine and 216 to placebo) were analyzed. This analysis was conducted from December 1, 2019, to September 1, 2020.
Interventions: Randomization to either levothyroxine or placebo.
Main outcomes and measures: Depressive symptom scores after 12 months measured with the Geriatric Depression Scale (GDS-15), with higher scores indicating more depressive symptoms (minimal clinically important difference = 2).
Results: A total of 427 participants with subclinical hypothyroidism (mean [SD] age, 74.52 [6.29] years; 239 women [56%]) were included in this analysis. The mean (SD) TSH level was 6.57 (2.22) mIU/L at baseline and decreased after 12 months to 3.83 (2.29) mIU/L in the levothyroxine group; in the placebo group, it decreased from 6.55 (2.04) mIU/L to 5.91 (2.66) mIU/L. At baseline, the mean (SD) GDS-15 score was 1.26 (1.85) in the levothyroxine group and 0.96 (1.58) in the placebo group. The mean (SD) GDS-15 score at 12 months was 1.39 (2.13) in the levothyroxine and 1.07 (1.67) in the placebo group with an adjusted between-group difference of 0.15 for levothyroxine vs placebo (95% CI, -0.15 to 0.46; P = .33). In a subgroup analysis including participants with a GDS-15 of at least 2, the adjusted between-group difference was 0.61 (95% CI, -0.32 to 1.53; P = .20). Results did not differ according to age, sex, or TSH levels. A previous meta-analysis (N = 278) on the association of levothyroxine with depressive symptoms was updated to include these findings, resulting in an overall standardized mean difference of 0.09 (95% CI, -0.05 to 0.22).
Conclusions and relevance: This ancillary study of a randomized clinical trial found that depressive symptoms did not differ after levothyroxine therapy compared with placebo after 12 months; thus, these results do not provide evidence in favor of levothyroxine therapy in older persons with subclinical hypothyroidism to reduce the risk of developing depressive symptoms.
Reference: Wildisen L et al. Effect of Levothyroxine Therapy on the Development of Depressive Symptoms in Older Adults With Subclinical Hypothyroidism: An Ancillary Study of a Randomized Clinical Trial. JAMA Netw Open. 2021 Feb 1;4(2):e2036645.

#7: Guideline: Almost all adults with SCH derive no benefit from thyroid hormone Rx

Clinical question What are the benefits and harms of thyroid hormones for adults with subclinical hypothyroidism (SCH)? This guideline was triggered by a recent systematic review of randomised controlled trials, which could alter practice.
Current practice Current guidelines tend to recommend thyroid hormones for adults with thyroid stimulating hormone (TSH) levels >10 mIU/L and for people with lower TSH values who are young, symptomatic, or have specific indications for prescribing.
Recommendation The guideline panel issues a strong recommendation against thyroid hormones in adults with SCH (elevated TSH levels and normal free T4 (thyroxine) levels). It does not apply to women who are trying to become pregnant or patients with TSH >20 mIU/L. It may not apply to patients with severe symptoms or young adults (such as those ≤30 years old).
How this guideline was created A guideline panel including patients, clinicians, and methodologists produced this recommendation in adherence with standards for trustworthy guidelines using the GRADE approach.
The evidence The systematic review included 21 trials with 2192 participants. For adults with SCH, thyroid hormones consistently demonstrate no clinically relevant benefits for quality of life or thyroid related symptoms, including depressive symptoms, fatigue, and body mass index (moderate to high quality evidence). Thyroid hormones may have little or no effect on cardiovascular events or mortality (low quality evidence), but harms were measured in only one trial with few events at two years' follow-up.
Understanding the recommendation The panel concluded that almost all adults with SCH would not benefit from treatment with thyroid hormones. Other factors in the strong recommendation include the burden of lifelong management and uncertainty on potential harms. Instead, clinicians should monitor the progression or resolution of the thyroid dysfunction in these adults. Recommendations are made actionable for clinicians and their patients through visual overviews. These provide the relative and absolute benefits and harms of thyroid hormones in multilayered evidence summaries and decision aids available in MAGIC (https://app.magicapp.org/) to support shared decisions and adaptation of this guideline.
Reference: Bekkering Et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

From BMJ

The systematic review included 21 trials with 2192 participants.

- For adults with SCH, thyroid hormones consistently demonstrate no clinically relevant benefits for:
    - quality of life
    - thyroid related symptoms
        - including depressive symptoms
        - fatigue
        - body mass index (moderate to high quality evidence).

- Thyroid hormones may have little or no effect on cardiovascular events or mortality (low quality evidence), but harms were measured in only one trial with few events at two years' follow-up.
- Instead, clinicians should monitor the progression or resolution of the thyroid dysfunction in these adults.

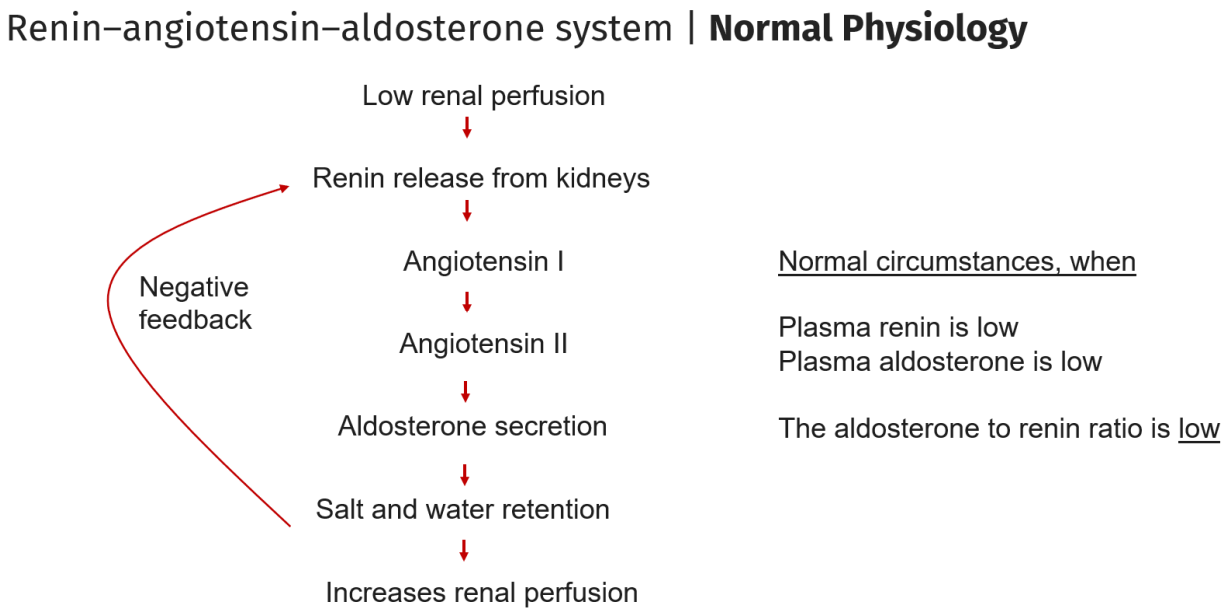
Among 58 706 patients with thyrotropin and FT4 or T4 levels available, levothyroxine was initiated for overt hypothyroidism in 8.4%, subclinical hypothyroidism in 61.0%, and normal thyroid levels in 30.5%.

Reference: Levothyroxine Use in the United States, 2008-2018. JAMA Intern Med. 2021;181(10):1402-1405.

Hyperaldosteronism

Primary aldosteronism, (AKA Conn syndrome), is a group of pathological conditions associated with an aldosterone secretion inappropriate for sodium intake, that is relatively autonomous from renin--angiotensin system activity and potassium levels."

Primary aldosteronism is widely recognized as the most common form of secondary hypertension



#8: Biochemically overt primary aldosteronism ranges between 11 and 22%

Background: Primary aldosteronism is a nonsuppressible renin-independent aldosterone production that causes hypertension and cardiovascular disease.
Objective: To characterize the prevalence of nonsuppressible renin-independent aldosterone production, as well as biochemically overt primary aldosteronism, in relation to blood pressure.
Design: Cross-sectional study.
Setting: 4 U.S. academic medical centers.
Participants: Participants with normotension (n = 289), stage 1 hypertension (n = 115), stage 2 hypertension (n = 203), and resistant hypertension (n = 408).
Measurements: Participants completed an oral sodium suppression test, regardless of aldosterone or renin levels, as a confirmatory diagnostic for primary aldosteronism and to quantify the magnitude of renin-independent aldosterone production. Urinary aldosterone was measured in participants in high sodium balance with suppressed renin activity. Biochemically overt primary aldosteronism was diagnosed when urinary aldosterone levels were higher than 12 µg/24 h.
Results: Every blood pressure category had a continuum of renin-independent aldosterone production, where greater severity of production was associated with higher blood pressure, kaliuresis, and lower serum potassium levels. Mean adjusted levels of urinary aldosterone were 6.5 µg/24 h (95% CI, 5.2 to 7.7 µg/24 h) in normotension, 7.3 µg/24 h (CI, 5.6 to 8.9 µg/24 h) in stage 1 hypertension, 9.5 µg/24 h (CI, 8.2 to 10.8 µg/24 h) in stage 2 hypertension, and 14.6 µg/24 h (CI, 12.9 to 16.2 µg/24 h) in resistant hypertension; corresponding adjusted prevalence estimates for biochemically overt primary aldosteronism were 11.3% (CI, 5.9% to 16.8%), 15.7% (CI, 8.6% to 22.9%), 21.6% (CI, 16.1% to 27.0%), and 22.0% (CI, 17.2% to 26.8%). The aldosterone–renin ratio had poor sensitivity and negative predictive value for detecting biochemically overt primary aldosteronism.
Limitation: Prevalence estimates rely on arbitrary and conventional thresholds, and the study population may not represent nationwide demographics.
Conclusion: The prevalence of primary aldosteronism is high and largely unrecognized. Beyond this categorical definition of primary aldosteronism, there is a prevalent continuum of renin-independent aldosterone production that parallels the severity of hypertension. These findings redefine the primary aldosteronism syndrome and implicate it in the pathogenesis of “essential” hypertension.
Reference: The Unrecognized Prevalence of Primary Aldosteronism. A Cross-sectional Study. Ann Intern Med. 2020 Oct 20;173(8):681-682.

- “Patients with apparent treatment-resistant hypertension are rarely tested for primary aldosteronism, despite guidelines recommending this practice”
- "Generally, failure to test patients with apparent treatment- resistant hypertension for primary aldosteronism may reflect a lack of familiarity with this common and treatable condition or a broader propensity for treatment inertia in this patient population." (Ann Intern Med. 2021 Mar;174(3):289-297)

#9: Testing for primary aldosteronism = rare among those with treatment resistant HTN

Background: Primary aldosteronism is a common cause of treatment-resistant hypertension. However, evidence from local health systems suggests low rates of testing for primary aldosteronism.
Objective: To evaluate testing rates for primary aldosteronism and evidence-based hypertension management in patients with treatment-resistant hypertension.
Design: Retrospective cohort study.
Setting: U.S. Veterans Health Administration.
Participants: Veterans with apparent treatment-resistant hypertension (n = 269 010) from 2000 to 2017, defined as either 2 blood pressures (BPs) of at least 140 mm Hg (systolic) or 90 mm Hg (diastolic) at least 1 month apart during use of 3 antihypertensive agents (including a diuretic), or hypertension requiring 4 antihypertensive classes.
Measurements: Rates of primary aldosteronism testing (plasma aldosterone–renin) and the association of testing with evidence-based treatment using a mineralocorticoid receptor antagonist (MRA) and with longitudinal systolic BP.
Results: 4277 (1.6%) patients who were tested for primary aldosteronism were identified. An index visit with a nephrologist (hazard ratio [HR], 2.05 [95% CI, 1.66 to 2.52]) or an endocrinologist (HR, 2.48 [CI, 1.69 to 3.63]) was associated with a higher likelihood of testing compared with primary care. Testing was associated with a 4-fold higher likelihood of initiating MRA therapy (HR, 4.10 [CI, 3.68 to 4.55]) and with better BP control over time.
Limitations: Predominantly male cohort, retrospective design, susceptibility of office BPs to misclassification, and lack of confirmatory testing for primary aldosteronism.
Conclusion: In a nationally distributed cohort of veterans with apparent treatment-resistant hypertension, testing for primary aldosteronism was rare and was associated with higher rates of evidence-based treatment with MRAs and better longitudinal BP control. The findings reinforce prior observations of low adherence to guideline-recommended practices in smaller health systems and underscore the urgent need for improved management of patients with treatment-resistant hypertension.
Reference: Testing for Primary Aldosteronism and Mineralocorticoid Receptor Antagonist Use Among U.S. Veterans. A Retrospective Cohort Study. Ann Intern Med. 2021 Mar;174(3):289-297

#10: Testing for primary aldosteronism = rare among those with HTN & hypokalemia

Primary aldosteronism is a common, yet highly underdiagnosed, cause of hypertension that leads to disproportionately high rates of cardiovascular disease. Hypertension plus hypokalemia is a guideline-recommended indication to screen for primary aldosteronism, yet

the uptake of this recommendation at the population level remains unknown. We performed a population-based retrospective cohort study of adults ≥18 years old in Ontario, Canada, with hypertension plus hypokalemia (potassium <3.5 mEq/L) from 2009 to 2015 with follow-up through 2017. We measured the proportion of individuals who underwent primary aldosteronism screening via the aldosterone-to-renin ratio based upon hypokalemia frequency and severity along with concurrent antihypertensive medication use. We assessed clinical predictors associated with screening via Cox regression. The cohort included 26 533 adults of which only 422 (1.6%) underwent primary aldosteronism screening. When assessed by number of instances of hypokalemia over a 2-year time window, the proportion of eligible patients who were screened increased only modestly from 1.0% (158/15 983) with one instance to 4.8% (71/1494) with ≥5 instances. Among individuals with severe hypokalemia (potassium <3.0 mEq/L), only 3.9% (58/1422) were screened. Among older adults prescribed ≥4 antihypertensive medications, only 1.0% were screened. Subspecialty care with endocrinology (hazard ratio [HR], 1.52 [95% CI, 1.10-2.09]), nephrology (HR, 1.43 [95% CI, 1.07-1.91]), and cardiology (HR, 1.39 [95% CI, 1.14-1.70]) were associated with an increased likelihood of screening, whereas age (HR, 0.95 [95% CI, 0.94-0.96]) and diabetes (HR, 0.66 [95% CI, 0.50-0.89]) were inversely associated with screening. In conclusion, population-level uptake of guideline recommendations for primary aldosteronism screening is exceedingly low. Increased education and awareness are critical to bridge this gap.
Reference: Screening Rates for Primary Aldosteronism Among Individuals With Hypertension Plus Hypokalemia: A Population-Based Retrospective Cohort Study. Hypertension. 2022 Jan;79(1):178-186.

#11: European Society of HTN Position Statement

Autonomous aldosterone overproduction represents the underlying condition of 5-10% of patients with arterial hypertension and carries a significant burden of mortality and morbidity. The diagnostic algorithm for primary aldosteronism is sequentially based on hormonal tests (screening and confirmation tests), followed by lateralization studies (adrenal CT scanning and adrenal venous sampling) to distinguish between unilateral and bilateral disease. Despite the recommendations of the Endocrine Society guideline, primary aldosteronism is largely underdiagnosed and undertreated with high between-centre heterogeneity. Experts from the European Society of Hypertension have critically reviewed the available literature and prepared a consensus document constituting two articles to summarize current knowledge on the epidemiology, diagnosis, treatment, and complications of primary aldosteronism.
Reference: Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. Journal of Hypertension. October 2020, Volume 38 (10), p 1919–1928

Primary Hyperaldosteronism | When To Screen

Subgroup	Recommendation to screen for primary aldosteronism	Comment
Therapy-resistant hypertension/grade 3 hypertension	Yes	Prevalence of PA increases with the severity of hypertension [5,6,31,32]
Hypertension at young age (<40 years old)	Probably, may require lower cut-offs	No data to confirm high prevalence/benefit in young patients with hypertension [33,34]
Hypokalemia	Yes	PA prevalence in patients affected by hypertension and serum K^+ <3.7 mmol/l is 28.1% and rises up to 88.5% in patients with spontaneous hypokalemia of less than 2.5 mmol/l [35]
Adrenal incidentaloma	Yes	Prevalence of PA in patients with adrenal incidentaloma is 1.6 to 4.33% [36,37][a]
Family history of PA/early stroke	Yes	Only in young, first-degree relatives with hypertension
Obstructive sleep apnea, obesity	No	The vast majority of patients with PA are tested for blood pressure levels grade at least 2 or hypokalemia [38]
Atrial fibrillation	Yes	If unexplained by structural heart disease and other conditions like hyperthyroidism [39]
Grade 2 hypertension	Yes	Especially if treatment response is poor; prevalence of PA increases with the severity of hypertension [5,6,31]
Grade 1 hypertension	Doubtful	Balance between costs and benefits should be considered

PA, primary aldosteronism.
[a]It must be acknowledged that the prevalence is calculated including also patients not affected by arterial hypertension and it is expected to double if considering only patients affected by arterial hypertension.

Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. Journal of Hypertension. October 2020, Volume 38 (10), p 1919–1928

Primary Hyperaldosteronism | How To Screen

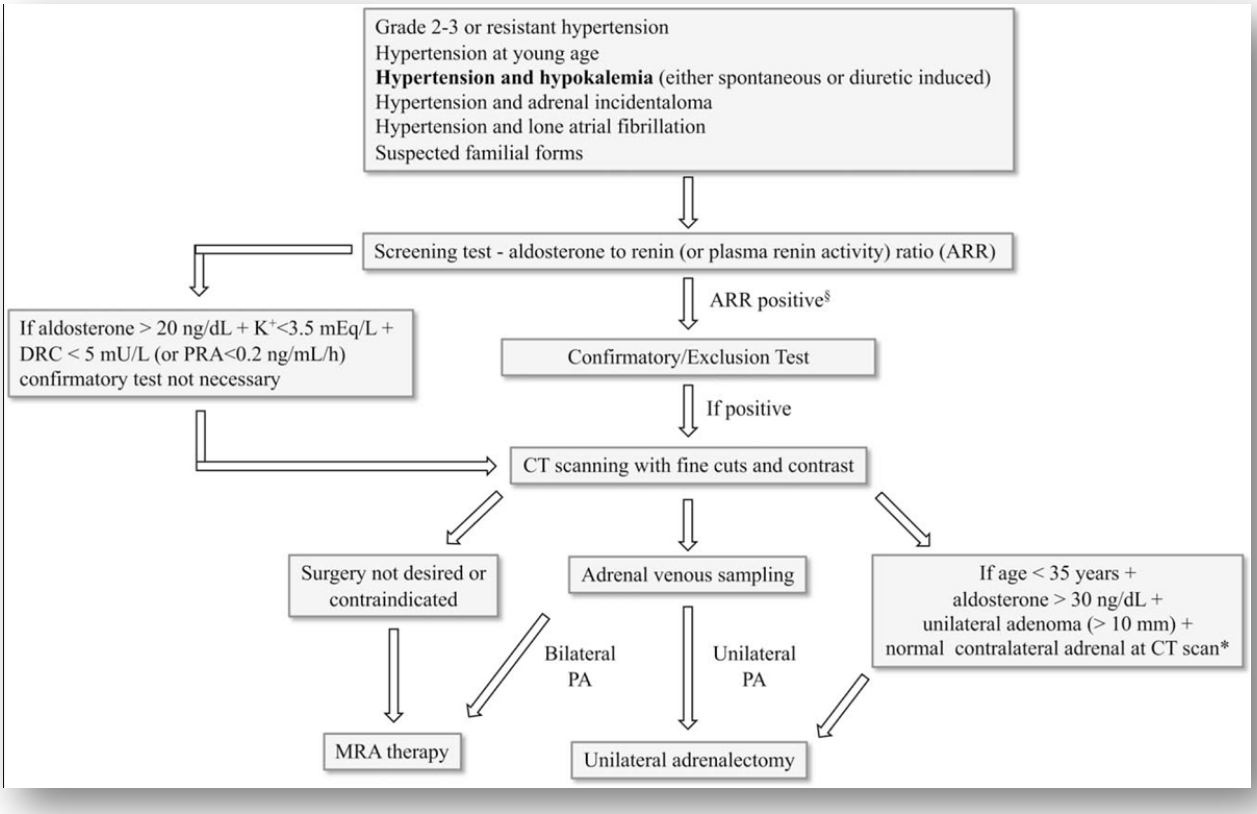
Measurement of plasma renin activity (PRA) and aldosterone concentration and calculation of the aldosterone to renin ratio (ARR) are the mainstay of PA screening work-up

- AM blood collection after patients have been out of bed for > 2 hours & seated for 5–15 minutes.
- Patients should have unrestricted dietary salt intake before testing and should be potassium-replete
- Not be taking drugs affecting the ARR (e.g., spironolactone, triamterene, amiloride, potassium-wasting diuretics) for > 4 weeks*

Suspect Primary Aldosteronism:

- PRA < 1 ng/mL/hr & PAC > 10 ng/dL

- Plasma aldosterone concentration (ng/dL) / Plasma renin activity (ng/mL/h) > 20



Male

Hypogonadism

Dx low testosterone | Total T < 300 ng/dL | 2 separate occasions | Early morning (fasting)
Low testosterone identified | Measure LH

- If T is low and LH is low or normal, measure prolactin and obtain an MRI
- If PRL = persistently high -> evaluate for endocrine disorders (prolactinoma)

Dx testosterone deficiency

- Low total T AND symptoms&/or signs

Male hypogonadism diagnosis is based upon the presence of signs and symptoms of male hypogonadism and unequivocally low serum total testosterone concentrations between 8 and 10 AM on at least two occasions

#12: Off-label testosterone prescriptions are common

Context: Testosterone replacement therapy (TRT) is currently approved by the Food and Drug Administration only for classic hypogonadism, although off-label indications have resulted in a dramatic expansion in prescriptions in the USA. Marketing may significantly affect prescriber behavior.
Objective: To systematically review all available evidence on marketing and TRT in the USA.
Evidence acquisition: PubMed, Embase, and Scopus were searched up to July 2017 for all relevant publications reporting on assessments of the TRT market size, economic costs associated with hypogonadism, trends in TRT prescriptions, drug discontinuation rates, and advertising and sales efforts in the USA.
Evidence synthesis: Twenty retrospective studies were included in the final analysis. The market size for hypogonadism constitutes 5.6-76.8% of men in the USA, with the lower end of the range representing the strictest criteria for diagnosis. Men with a diagnosis of hypogonadism consume $14 118 in direct and indirect costs to the payer. Over the last 2 decades, TRT prescriptions have increased between 1.8- and 4-fold. After 1 yr, 80-85% of men discontinue TRT. There is an association between direct-to-consumer advertising and testosterone testing, TRT prescriptions, and TRT without testosterone testing. There is a high prevalence of misinformation on Internet advertising.

Conclusions: Off-label indications have driven the dramatic expansion of TRT prescriptions over the last 2 decades. Direct-to-consumer advertising poses a unique challenge in the USA. Overtreatment can be avoided by applying strict diagnostic criteria for hypogonadism, which limits the addressable market for TRT.
Patient summary: In this report, we reviewed the relationship between marketing and testosterone therapy in the USA. We found that many patients are prescribed testosterone without an appropriate diagnosis of hypogonadism, which may be related to the marketing efforts for off-label prescribing.
Reference: Marketing and Testosterone Treatment in the USA: A Systematic Review. Eur Urol Focus 2017 Oct;3(4-5):395-402.

#13: Adult-onset low T assoc with sexual dysfunction

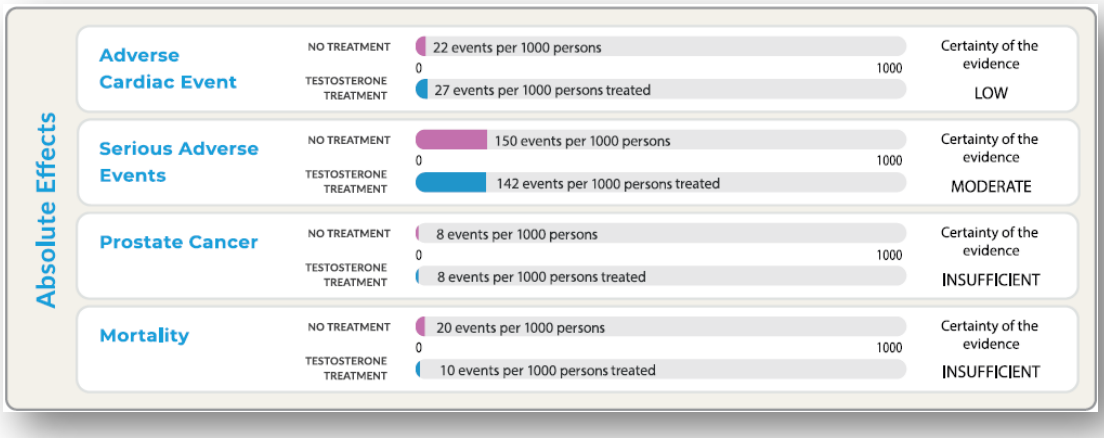
Background: The association between aging-related testosterone deficiency and late-onset hypogonadism in men remains a controversial concept. We sought evidence-based criteria for identifying late-onset hypogonadism in the general population on the basis of an association between symptoms and a low testosterone level.
Methods: We surveyed a random population sample of 3369 men between the ages of 40 and 79 years at eight European centers. Using questionnaires, we collected data with regard to the subjects' general, sexual, physical, and psychological health. Levels of total testosterone were measured in morning blood samples by mass spectrometry, and free testosterone levels were calculated with the use of Vermeulen's formula. Data were randomly split into separate training and validation sets for confirmatory analyses.
Results: In the training set, symptoms of poor morning erection, low sexual desire, erectile dysfunction, inability to perform vigorous activity, depression, and fatigue were significantly related to the testosterone level. Increased probabilities of the three sexual symptoms and limited physical vigor were discernible with decreased testosterone levels (ranges, 8.0 to 13.0 nmol per liter [2.3 to 3.7 ng per milliliter] for total testosterone and 160 to 280 pmol per liter [46 to 81 pg per milliliter] for free testosterone). However, only the three sexual symptoms had a syndromic association with decreased testosterone levels. An inverse relationship between an increasing number of sexual symptoms and a decreasing testosterone level was observed. These relationships were independently confirmed in the validation set, in which the strengths of the association between symptoms and low testosterone levels determined the minimum criteria necessary to identify late-onset hypogonadism.
Conclusions: Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per liter (3.2 ng per milliliter) and a free testosterone level of less than 220 pmol per liter (64 pg per milliliter).
Reference: Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010 Jul 8;363(2):123-35.

#14: TRT assoc with slight improvement in sexual function

Context: The efficacy and safety of testosterone replacement therapy (TRT) in hypogonadal men remain incompletely understood.
Objective: To conduct a systematic review and meta-analysis of randomized clinical trials (RCTs) to determine the effects of TRT on patient important outcomes and adverse events in hypogonadal men.
Data Sources: We searched Ovid Medline, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus, from inception to 2 March 2017.
Study Selection: Randomized clinical trials assessing the efficacy and adverse events of TRT of at least 12 weeks compared with placebo in adult men with hypogonadism, defined by morning total testosterone ≤300 ng/dL and at least one symptom or sign of hypogonadism.
Data Extraction: Reviewers working independently and in duplicate assessed the quality of RCTs and collected data on patient characteristics, interventions, and outcomes.
Results: We found four RCTs (including 1779 patients) at low risk of bias. Compared with placebo, TRT was associated with a small but significant increase in sexual desire or libido [standardized mean difference (SMD): 0.17; 95% confidence interval (CI), 0.01, 0.34; n = 1383], erectile function (SMD: 0.16; 95% CI, 0.06, 0.27; n = 1344), and sexual satisfaction (SMD: 0.16; 95% CI, 0.01, 0.31; n = 676) but had no effect on energy or mood. TRT was associated with an increased risk of developing erythrocytosis (relative risk: 8.14; 95% CI, 1.87, 35.40; n = 1579) compared with placebo but had no significant effect on lower urinary tract symptoms.
Conclusion: in hypogonadal men, TRT improves sexual desire, erectile function and sexual satisfaction; however, it increases the risk of erythrocytosis.
Reference: The Efficacy and Adverse Events of Testosterone Replacement Therapy in Hypogonadal Men: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials. J Clin Endocrinol & Metabol Vol 103, Issue 5, May 2018, Pages 1745–1754,

#15: Testosterone Rx for age-related low T | ACP Guideline

Recommendation 1a: Discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function (conditional recommendation; low-certainty evidence).
Recommendation 1b: Reevaluate symptoms within 12 months … discontinue testosterone … if no improvement in sexual function (conditional recommendation; low-certainty evidence).
Recommendation 1c: Consider intramuscular rather than transdermal formulations … costs are considerably lower for the intramuscular formulation and clinical effectiveness and harms are similar.
Recommendation 2: Do not initiate testosterone treatment in men with age related low testosterone to improve energy, vitality, physical function, or cognition (conditional recommendation. low-certainty evidence).
Reference: Testosterone Treatment in Adult Men With Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians. Ann Intern Med. 2020 Jan 21;172(2):126-133.



Bottom-Lines

- There is no discernable benefit of treating subclinical hypothyroidism in most adults
- Hyperaldosteronism is common; looking for it is not common
- Symptomatically, low T is associated with sexual dysfunction & not associated with energy, mood
- T replacement associated with improved sexual function at the cost of a higher risk of erythrocytosis

Liver and GI Update — Henry C. Barry, MD, MS

Objectives: At the end of this session, the participant will be able to:

- describe approaches to managing persons with diarrhea
- summarize recent research on screening and managing patients with hepatitis C
- describe a comprehensive approach to managing patients with irritable bowel syndrome

Acute gastroenteritis in children

1. Oral ondansetron decreases vomiting in children with acute gastroenteritis

Clinical question: Is ondansetron effective in decreasing vomiting in children with acute gastroenteritis?
Study design: Randomized controlled trial (nonblinded) **Funding source:** Government **Setting:** Outpatient (primary care)
Synopsis: For this pragmatic trial in primary care settings, the investigators enrolled 175 children with acute gastroenteritis who were at risk of dehydration (aged 6 months to 6 years with 4 or more episodes of vomiting within 24 hours and at least 1 episode of vomiting within 4 hours of presentation). The researchers randomized the children to receive control therapy (oral rehydration therapy of 10 mL/kg unless the clinician thought they child was already dehydrated, in which case they used 15 mL/kg for 4 hours) or oral ondansetron syrup (0.1 mg/kg; administered as a single dose and repeated only once if the child vomited within 15 minutes of administration). The parents completed symptom diaries hourly for the first 4 hours after presentation, then once daily for 1 week. Fewer ondansetron-treated children continued to vomit within the first 4 hours after randomization (19.5% vs. 42.9%; number needed to treat = 5; 95% CI 4 - 15); however, the rate of referrals to the emergency department (19.4%) and hospitalizations (14.4%) were not significantly decreased. Although the rate of adverse events (31.3%) and serious adverse events (6.6%) were similar between the 2 groups, parental satisfaction was slightly higher among the children treated with ondansetron.
Bottom line: Oral ondansetron decreases vomiting in children with acute gastroenteritis, but does not decease hospitalizations or referrals to emergency departments.
Bonvanie IJ, Weghorst AA, Holtman GA, et al. Oral ondansetron for paediatric gastroenteritis in primary care: a randomised controlled trial. Br J Gen Pract 2021;71(711):e728-e735.

2. Oral ginger is an effective antiemetic in children with gastroenteritis

Clinical question: Does ginger reduce vomiting in children with acute gastroenteritis?
Study design: Randomized controlled trial (double-blinded) **Funding source:** Industry + foundation
Synopsis: Investigators enrolled children 1 to 10 years old (average 5.5 years) who presented to pediatricians with acute gastroenteritis, symptom duration of less than 12 hours, and an average of 4 vomiting episodes within the previous 4 hours. The children had mild to moderate dehydration. The 150 children were randomized, using concealed allocation, to receive 10 mg ginger or placebo (both in liquid form, matched to color and taste) at the time of evaluation and every 8 hours if vomiting continued. All children also received an oral rehydration solution 30 minutes after the first dose. Using per-protocol analysis (i.e., only evaluating children who received the first dose), the ginger prevented further vomiting over the subsequent 8 hours in 36% of children as compared with 14% of children who received the placebo (P = .002; number needed to treat = 5; 95% CI 3 - 14). Results were similar when analyzed by intention to treat. More than 24 hours after the first dose, 86% of children who received the placebo experienced at least one episode of vomiting as compared with 64% of children who received ginger. There were no side effects in either group.
Bottom line: Ginger, in liquid form, stopped vomiting in children who presented with acute gastroenteritis. This rate of effectiveness is similar to emergency department administration of ondansetron (Zofran). The liquid form of ginger may be difficult to find — ginger ale soft drinks contain little to no ginger — and I would be concerned about using the more common ginger lozenge in young children. But given its low cost and lack of side effects, a liquid form of ginger (if you can find it) may be a good option for at-home management of mild-to-moderate acute gastroenteritis in children and allow them to keep oral rehydration solutions down.
Nocerino R, Cecere G, Micillo M, et al. Efficacy of ginger as antiemetic in children with acute gastroenteritis: a randomised controlled trial. Aliment Pharmacol Ther 2021;54(1):24-31.

Lower GI

3. Fecal calprotectin is accurate in identifying kids with inflammatory bowel disease in primary care

Clinical question: How accurate is fecal calprotectin testing in identifying children with inflammatory bowel disease in primary care?
Study design: Cohort (prospective) **Setting:** Outpatient (primary care)
Synopsis: These researchers enrolled 195 children between the ages of 4 years and 18 years with gastrointestinal problems whose primary care clinician decided to perform a fecal calprotectin assay. They excluded children with an established IBD diagnosis, those who were suspected of having cancer, and those who had used nonsteroidal anti-inflammatory drugs. The authors used a quantitative ELISA-based fecal calprotectin assay. Levels of 100 mcg/g and higher were considered positive. The gold standard for IBD diagnosis was based on clinical, radiologic, and histopathologic findings during the 12 months after the index assay. Nearly half the children (46%) were female and slightly more than half (54%) had at least one "red flag" criterion for IBD (e.g., rectal bleeding, nocturnal symptoms, and so forth). Approximately half the time, the treating clinician would have referred the child if the fecal calprotectin assay were not available. Thirteen (7%) children were ultimately given a diagnosis of IBD: 8 had Crohn's disease, 2 had ulcerative colitis, and 3 were unclassified. The authors report that fecal calprotectin was 100% sensitive (95% CI 75% - 100%) and 91% specific (85% - 94%), which translates to a positive likelihood ratio of 11.1 (5 - 16.7) and a negative likelihood ratio of 0 (0 - 0.3). In other words, this is a pretty decent test for ruling out IBD. However, in a low-prevalence setting, even a specific test carries a greater than 50% false positive rate. The fecal calprotectin test result modestly influenced clinician behavior: 83% of the patients with positive fecal calprotectin levels were referred compared with 54% of those with negative levels.

Bottom line: In this study, primary care–based testing of fecal calprotectin was reasonably accurate in identifying which children with gastrointestinal symptoms should be referred for diagnosis. When the fecal calprotectin result is negative, it effectively rules out inflammatory bowel disease (IBD).
Walker GJ, Chanchlani N, Thomas A, et al. Primary care faecal calprotectin testing in children with suspected inflammatory bowel disease: a diagnostic accuracy study. Arch Dis Child 2020;105(10):957-963.

4. Guideline for chronic diarrhea: screening for IBD and celiac disease is in, screening for ova and parasites is out

Clinical question: What work-up should be considered for patients with chronic diarrhea?
Study design: Practice guideline
Synopsis: This guideline, from the American Gastroenterological Association, was developed by a team comprising 2 gastroenterologists, a primary care physician, and a methodologist, but no patient representative. They performed a systematic review and graded the level of evidence using the GRADE rubric. One team member reported financial relationships with companies that make diagnostic or treatment products for gastrointestinal disorders. In patients with chronic diarrhea, the group suggests screening for IBD using fecal calprotectin or fecal lactoferrin, but not ESR or CRP (conditional recommendation based on low-quality evidence). They also recommend testing for giardia (strong recommendation, high-quality evidence), but recommend against testing for ova or other parasites unless the patient is from or has traveled to a high-risk area (conditional recommendation, low-quality evidence). They also suggest testing for celiac disease (strong recommendation, moderate-quality evidence) and testing for bile acid diarrhea by assay or by an empiric trial of a bile acid binder (conditional recommendation, low-quality evidence). Unfortunately, the group does not recommend a specific order of testing.
Bottom line: Though not offering an algorithm to guide the work-up, the American Gastroenterological Association suggests the following tests for patients with chronic diarrhea (i.e., watery diarrhea for at least 4 weeks): fecal calprotectin or fecal lactoferrin to screen for inflammatory bowel disease (IBD), and testing for giardiasis, celiac disease, and bile acid diarrhea. They recommend not screening for ova and parasites unless the patient has come from a high-risk area. They also recommend against using erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to screen for IBD.
Smalley W, Falck-Ytter C, Carrasco-Labra A, Wani S, Lytvyn L, Falck-Ytter Y. AGA clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology 2019;157(3):851-854.

5. ACG guideline on the prevention, diagnosis, and treatment of Clostridioides difficile infections

Clinical question: How should clinicians prevent *Clostridioides difficile* (*C. difficile;* previously known as *Clostridium difficile*) infections and treat persons with *C. difficile*?
Study design: Practice guideline
Synopsis: This is an update of the ACG 2013 guideline. Unlike previous ACG guidelines, this report does not describe much about the development process or the panel membership, other than their use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to grade the strength of the recommendations and the quality of the evidence. The following table summarizes some of the key recommendations that are likely to be relevant in primary care. The body of the guideline contains useful resources such as dosing guidelines, as well as indications for surgery, management of persons with comorbid inflammatory bowel disease, and those with refractory infections.

Type of Recommendation	Intervention
Strongly in favor	Oral vancomycin, fidaxomicin, or metronidazole for treating persons with nonsevere infections
	Oral vancomycin or fidaxomicin for treating those with severe infections
	Fluid resuscitation plus oral vancomycin +/- parenteral metronidazole for patients with fulminant infections
	Fecal microbiota transplant in persons with severe and fulminant *C. difficile* infection refractory to antibiotic therapy and to prevent recurrence in those experiencing their second (or more) *C. difficile* infection
Conditionally in favor	Testing algorithms should use highly sensitive and highly specific tests to distinguish colonization from active infection
	Vancomycin enemas in persons with ileus
	Repeat fecal microbiota transplant for persons experiencing a recurrence within 8 weeks of an initial transplant
Conditionally against	Use of probiotics to prevent *C. difficile* in persons taking antibiotics
Strongly against	Use of probiotics to prevent recurrence

Bottom line: The American College of Gastroenterology (ACG) generally recommends against the use of probiotics to prevent *C. difficile* infections either in persons taking antibiotics or those with recurrent infections. Additionally, it recommends various oral antibiotics (vancomycin, fidaxomicin, or metronidazole) for treating active infections and the use of fecal microbiota transplantation in persons with severe or fulminant infections refractory to antibiotics or to prevent recurrent infections.
Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of Clostridioides difficile infections. Am J Gastroenterol 2021;116(6):1124-1147.

6. Cancer found in fewer than 1% of patients after uncomplicated diverticulitis

Clinical question: How often are colorectal neoplasms detected in patients undergoing colonoscopy after acute left-sided diverticulitis?
Study design: Meta-analysis (other) **Setting:** Various (meta-analysis)
Synopsis: These authors searched PubMed and EMBASE to identify studies that evaluated neoplasm detection by colonoscopy in patients within one year of CT-confirmed acute left-sided diverticulitis. They did not describe searching for unpublished studies, and explicitly excluded reviews, conference abstracts, letters to the editor, animal studies, and studies with fewer than 10 patients. Two authors independently evaluated studies for inclusion and evaluated the included studies for risk of bias. They settled discrepancies by discussion. They describe using a random-effects model to estimate the prevalence rates of advanced colonic neoplasm and colorectal carcinoma. This will generate slightly more conservative estimates and wider confidence intervals, and is probably appropriate in light of the variability one might expect to find among the various studies. Ultimately, the authors included 17 studies with 3296 patients, 959 of whom had uncomplicated cases of diverticulitis. Four studies were prospective cohorts and 13 were retrospective. Four studies only included patients with left-sided diverticulitis; the remainder did not report the proportion of patients with left-sided disease. The authors point out that these studies took place in the Western world where they claim "the vast majority" of cases are left-sided. Eight of the studies excluded patients who had colonoscopy before the onset of acute diverticulitis (6 months to 2 years). The authors rated the quality of the studies as moderate to good. Only 2 studies had a comparison group of asymptomatic patients, and reported no statistically significant increased risk of colorectal carcinoma among the afflicted patients. Overall, the pooled rate of colorectal carcinoma was 2.1% (95% CI 1.5 - 3.1). Among patients with uncomplicated events, the pooled rate was 0.5% (0.2 - 1.2) and among those with complicated cases (accompanied by abscess, perforation, or fistula) the pooled rate was 8.3% (4.2 - 15.8). Finally, the rate of advanced colorectal neoplasia was 6.9% (5.9 - 9.4). Among the studies that reported the location of the neoplasms, 41 of 43 were at the site of presumed diverticulitis. We commonly find that harms are not reported, and in this case only 4 studies reported them: 3 perforations among 683 procedures.
Bottom line: Among patients previously adequately screened for colorectal carcinoma, it is uncommon to find colorectal neoplasms within one year of an episode of acute left-sided diverticulitis confirmed by computed tomography (CT). Among those with uncomplicated events, the rate of carcinoma is well under 1%.
Rottier SJ, van Dijk ST, van Geloven AAW, et al. Meta-analysis of the role of colonoscopy after an episode of left-sided acute diverticulitis. Br J Surg 2019;106(8):988-997.

Appendicitis

7. New clinical prediction rule (the Pediatric Appendicitis Laboratory Score) accurately rules out appendicitis in children

Clinical question: Can a combination of clinical features and laboratory values rule out acute appendicitis in children?
Study design: Decision rule (validation) **Setting:** Emergency department
Synopsis: These authors prospectively enrolled children 2 years to 14 years of age who visited a single emergency department for suspected appendicitis. The research team gathered clinical and laboratory data in a structured manner. From the 361 children they enrolled, the authors randomly selected 278 to develop a clinical prediction rule, and then validated the rule on a mixed cohort of the 83 remaining children an additional 172 children seen in the same emergency department during an earlier time frame. The diagnosis of appendicitis was confirmed using pathology for those undergoing surgery and clinical follow-up 15 days after the index visit. Clouding the picture a bit, the authors also used ultrasound during the diagnostic process. Among the children in the derivation cohort, 35.9% had acute appendicitis compared with 49% in the validation group. After performing feats of statistical gymnastics, the authors created the PALabS, which consists of 6 parts: nausea (3 points), maximal pain in the right lower quadrant (4 points), absolute neutrophil count above 7500 per microliter (7 points), white blood cell count above 10,000 per microliter (4 points), C-reactive protein above 10 mg per liter (2 points), and calprotectin above 50 nanograms per milliliter (3 points). Overall, in the derivation group, the PALabS was accurate (area under the receiver operator characteristic curve 0.88). The researchers also applied 2 other scores to the derivation sample, the Pediatric Appendicitis Score and the Kharbanda Score. They found these scores to have less diagnostic accuracy. In the validation cohort, a PALabS of 6 or less was 99.2% sensitive (95% CI 95.6 - 99.9) and had a negative likelihood ratio of 0.03 (0.00 - 0.18). Although the authors did not report the specificity of the PALabS, based on my calculations, it was approximately 32% and the positive likelihood ratio was 3.2. In other words, this looks like a SnNOut (a very sensitive test that rules out the disease when the result result is negative). Now this clinical prediction rule needs to be tested in an independent cohort of patients.
Bottom line: The Pediatric Appendicitis Laboratory Score (PALabS), a score that combines clinical features and laboratory values, is accurate in ruling out acute appendicitis in children.
Benito J, Fernandez S, Gendive M, et al. A new clinical score to identify children at low risk for appendicitis. Am J Emerg Med 2020;38(3):554-561.

8. Point-of-care ultrasound in the ED is pretty accurate for diagnosis of appendicitis

Clinical question: Is point-of-care ultrasound accurate in the diagnosis of acute appendicitis?
Study design: Meta-analysis (other) **Setting:** Emergency department
Synopsis: These authors searched 2 databases and the bibliographies of the included articles to identify studies that studied children and adults with right lower quadrant pain evaluated with POCUS and used surgical findings as the gold standard. Two investigators independently assessed studies for inclusion. They also assessed the risk of bias for the included studies and resolved disagreements through discussion. The authors included a total of 17 studies with 2385 patients. In 3 of the studies, an appendix diameter greater than 7 mm was the criterion for appendicitis; the other 14 studies used 6 mm. The included studies were generally of low to moderate risk of bias; none were seriously flawed. The range of appendicitis was 24% to 75%. Overall, POCUS had decent sensitivity (84%; 95% CI 72% - 92%) and specificity (91%; 85% - 95%), which translates to a positive likelihood ratio (LR+) of 9.3 (4.8 - 18.4) and a negative likelihood ratio (LR-) of 0.18 (0.08 - 0.33). In children, POCUS was even better: 95% sensitivity (75% - 99%), 95% specificity (85% - 98%), LR+ 19.4 (5 - 99), and LR- 0.05 (0.01 - 0.29). The authors found, however, significant heterogeneity in the data. Finally, in the studies that compared POCUS with radiologist-performed ultrasound, the authors found no significant difference in accuracy.

Bottom line: Point-of-care ultrasound (POCUS) is reasonably accurate in diagnosing acute appendicitis.
Lee SH, Yun SJ. Diagnostic performance of emergency physician-performed point-of-care ultrasonography for acute appendicitis: A meta-analysis. Am J Emerg Med 2019;37(4):696-705.

9. Quality of life after antibiotics = surgery for appendicitis, but 30% still require surgery in 90 days

Clinical question: As compared with surgery, does treatment with antibiotics for acute appendicitis affect quality of life at 30 days?
Study design: Randomized controlled trial (nonblinded) **Setting:** Inpatient (any location)
Synopsis: Although 95% of patients in the United States with appendicitis undergo appendectomy, antibiotic therapy is an alternative treatment. These investigators randomized adults presenting to emergency departments with acute appendicitis (confirmed by imaging) to receive either antibiotic therapy or surgery. Patients with septic shock, diffuse peritonitis, complicated or recurrent appendicitis, or evidence of cancer were excluded. Patients in the antibiotic group (n = 776) received an intravenous antibiotic for at least 24 hours, followed by an oral antibiotic, for a 10-day total course. Patients in the surgery group (n = 776) underwent appendectomy, mostly laparascopic, followed by routine postoperative care. The 2 groups had similar socioeconomic and clinical characteristics at baseline. The primary outcome, a standard quality of life measure, was statistically similar in the 2 groups at 30 days, consistent with noninferiority of antibiotics to surgery. The antibiotic group has fewer missed work days (5.26 days vs 8.73 days), but more visits to the emergency department (9% vs 4%) and more hospitalizations (24% vs 5%) within 90 days of the index treatment. Overall, 29% of the antibiotic group underwent surgery by 90 days. A subgroup of patients with appendicoliths had similar quality of life results when comparing antibiotic treatment with surgery. However, when compared with patients without appendicoliths, these patients were more likely to require appendectomy at 90 days (41% vs 25%) and have a higher rate of complications (20.2 vs 3.6 per 100 participants).
Bottom line: Antibiotics are an effective alternative, as compared with surgery, for the treatment of acute appendicitis with regard to short-term quality of life. Although patients managed with antibiotics required more health care visits following treatment, 70% were able to avoid surgery within 90 days. A subset of patients with appendicoliths were more likely to require appendectomy and have complications following antibiotic treatment. These patients may need further consideration for initial surgical treatment.
The CODA Collaborative, Flum DR, Davidson GH, et al. A randomized trial comparing antibiotics with appendectomy for appendicitis. N Engl J Med 2020;383(20):1907-1919.

Hepatitis C

10. USPSTF 2020 recommends screening for hepatitis C virus infection in adolescents and adults aged 18 to 79 (B recommendation)

Clinical question: Should primary care clinicians screen for the hepatitis C virus in asymptomatic adolescents and adults aged 18 years to 79 years?
Study design: Practice guideline **Funding source:** Government
Synopsis: In this updated review, the task force found no direct evidence of a benefit of screening for HCV infection on patient-oriented outcomes. The task force did find that the current screening regimen accurately detects HCV infection. In addition, current treatment protocols are very effective and safe at achieving an SVR in greater than 95% of patients aged 18 years to 79 years. Finally, the available evidence shows a consistent association between SVR and improved patient-oriented outcomes, including a reduction in all-cause mortality, cirrhosis, and hepatocellular carcinoma. The potential harms of screening include patient anxiety and labeling, but the task force concluded that the overall net benefit is substantial. The Centers for Disease Control and Prevention and the Infectious Disease Society of America recommend at least one screening for HCV infection in all adults 18 years and older.
Bottom line: In this updated 2020 review, the U.S. Preventive Services Task Force (USPSTF) found adequate evidence that hepatitis C virus (HCV) screening accurately detects HCV infection. Although there is no direct evidence on the benefit of screening for HCV infection on patient-oriented outcomes, there is convincing evidence that treatment results in a high proportion (95.5% - 98.9%) of adults who maintain a sustained virologic response (SVR), with a strong association between SVR and improved health outcomes. The task force also recommends screening for HCV in all pregnant women. These recommendations replace the previous 2013 USPSTF recommendation of screening adults born between 1945 and 1965.
US Preventive Services Task Force. Screening for hepatitis C virus infection in adolescents and adults. US Preventive Services Task Force recommendation statement. JAMA 2020;323(10):970-975.

11. Direct-acting antivirals for chronic hepatitis C

Background: Millions of people worldwide suffer from hepatitis C, which can lead to severe liver disease, liver cancer, and death. Direct-acting antivirals (DAAs), e.g. sofosbuvir, are relatively new and expensive interventions for chronic hepatitis C, and preliminary results suggest that DAAs may eradicate hepatitis C virus (HCV) from the blood (sustained virological response). Sustained virological response (SVR) is used by investigators and regulatory agencies as a surrogate outcome for morbidity and mortality, based solely on observational evidence. However, there have been no randomised trials that have validated that usage. **Objectives:** To assess the benefits and harms of DAAs in people with chronic HCV.
Search methods: We searched for all published and unpublished trials in The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, LILACS, and BIOSIS; the Chinese Biomedical Literature Database (CBM), China Network Knowledge Information (CNKI), the Chinese Science Journal Database (VIP), Google Scholar, The Turning Research into Practice (TRIP) Database, ClinicalTrials.gov, European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trials Registry Platform (www.who.int/ictrp), the Food and Drug Administration (FDA) (www.fda.gov), and pharmaceutical company sources for ongoing or unpublished trials. Searches were last run in October 2016. **Selection criteria:** Randomised clinical trials comparing DAAs versus no intervention or placebo, alone or with co-interventions, in adults with chronic HCV. We included trials irrespective of publication type, publication status, and language. **Data collection and analysis:** We used standard methodological procedures expected by Cochrane. Our primary outcomes were hepatitis C-related morbidity, serious adverse events, and health-related quality of life. Our secondary outcomes were all-cause mortality, ascites, variceal bleeding, hepato-renal

syndrome, hepatic encephalopathy, hepatocellular carcinoma, non-serious adverse events (each reported separately), and SVR. We systematically assessed risks of bias, performed Trial Sequential Analysis, and followed an eight-step procedure to assess thresholds for statistical and clinical significance. We evaluated the overall quality of the evidence, using GRADE.
Main results: We included a total of 138 trials randomising a total of 25,232 participants. The trials were generally short-term trials and designed primarily to assess the effect of treatment on SVR. The trials evaluated 51 different DAAs. Of these, 128 trials employed matching placebo in the control group. All included trials were at high risk of bias. Eighty-four trials involved DAAs on the market or under development (13,466 participants). Fifty-seven trials administered DAAs that were discontinued or withdrawn from the market. Study populations were treatment-naive in 95 trials, had been exposed to treatment in 17 trials, and comprised both treatment-naive and treatment-experienced individuals in 24 trials. The HCV genotypes were genotype 1 (119 trials), genotype 2 (eight trials), genotype 3 (six trials), genotype 4 (nine trials), and genotype 6 (one trial). We identified two ongoing trials.
We could not reliably determine the effect of DAAs on the market or under development on our primary outcome of hepatitis C-related morbidity or all-cause mortality. There were no data on hepatitis C-related morbidity and only limited data on mortality from 11 trials (DAA 15/2377 (0.63%) versus control 1/617 (0.16%); OR 3.72, 95% CI 0.53 to 26.18, very low-quality evidence). We did not perform Trial Sequential Analysis on this outcome.
There is very low quality evidence that DAAs on the market or under development do not influence serious adverse events (DAA 5.2% versus control 5.6%; OR 0.93, 95% CI 0.75 to 1.15 , 15,817 participants, 43 trials). The Trial Sequential Analysis showed that there was sufficient information to rule out that DAAs reduce the relative risk of a serious adverse event by 20% when compared with placebo. The only DAA that showed a lower risk of serious adverse events when meta-analysed separately was simeprevir (OR 0.62, 95% CI 0.45 to 0.86). However, Trial Sequential Analysis showed that there was not enough information to confirm or reject a relative risk reduction of 20%, and when one trial with an extreme result was excluded, the meta-analysis result showed no evidence of a difference.
DAAs on the market or under development may reduce the risk of no SVR from 54.1% in untreated people to 23.8% in people treated with DAA (RR 0.44, 95% CI 0.37 to 0.52, 6886 participants, 32 trials, low quality evidence). Trial Sequential Analysis confirmed this meta-analysis result.
Only 1/84 trials on the market or under development assessed the effects of DAAs on health-related quality of life (SF-36 mental score and SF-36 physical score).
There was insufficient evidence from trials on withdrawn or discontinued DAAs to determine their effect on hepatitis C-related morbidity and all-cause mortality (OR 0.64, 95% CI 0.23 to 1.79; 5 trials, very low-quality evidence). However, these DAAs seemed to increase the risk of serious adverse events (OR 1.45, 95% CI 1.22 to 1.73; 29 trials, very low-quality evidence). Trial Sequential Analysis confirmed this meta-analysis result.
None of the 138 trials provided useful data to assess the effects of DAAs on the remaining secondary outcomes (ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, and hepatocellular carcinoma).
Authors' conclusions: The evidence for our main outcomes of interest come from short-term trials, and we are unable to determine the effect of long-term treatment with DAAs. The rates of hepatitis C morbidity and mortality observed in the trials are relatively low and we are uncertain as to how DAAs affect this outcome. Overall, there is very low quality evidence that DAAs on the market or under development do not influence serious adverse events. There is insufficient evidence to judge if DAAs have beneficial or harmful effects on other clinical outcomes for chronic HCV. Simeprevir may have beneficial effects on risk of serious adverse event. In all remaining analyses, we could neither confirm nor reject that DAAs had any clinical effects. DAAs may reduce the number of people with detectable virus in their blood, but we do not have sufficient evidence from randomised trials that enables us to understand how SVR affects long-term clinical outcomes. SVR is still an outcome that needs proper validation in randomised clinical trials.
Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, Poropat G, Djurisic S, Weiss KH, Bjelakovic M, Bjelakovic G, Klingenberg SL, Liu JP, Nikolova D, Koretz RL, Gluud C. Direct-acting antivirals for chronic hepatitis C. Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012143. DOI: 10.1002/14651858.CD012143.pub3.

12. Pharmacological interventions for acute hepatitis C infection

Background: Hepatitis C virus (HCV) is a single-stranded RNA (ribonucleic acid) virus that has the potential to cause inflammation of the liver. The traditional definition of acute HCV infection is the first six months following infection with the virus. Another commonly used definition of acute HCV infection is the absence of HCV antibody and subsequent seroconversion (presence of HCV antibody in a person who was previously negative for HCV antibody). Approximately 40% to 95% of people with acute HCV infection develop chronic HCV infection, that is, have persistent HCV RNA in their blood. In 2010, an estimated 160 million people worldwide (2% to 3% of the world's population) had chronic HCV infection. The optimal pharmacological treatment of acute HCV remains controversial. Chronic HCV infection can damage the liver. **Objectives:** To assess the comparative benefits and harms of different pharmacological interventions in the treatment of acute HCV infection through a network meta-analysis and to generate rankings of the available pharmacological treatments according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and instead we assessed the comparative benefits and harms of different interventions versus each other or versus no intervention using standard Cochrane methodology. **Search methods:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and randomised controlled trials registers to April 2016 to identify randomised clinical trials on pharmacological interventions for acute HCV infection. **Selection criteria:** We included only randomised clinical trials (irrespective of language, blinding, or publication status) in participants with acute HCV infection. We excluded trials which included previously liver transplanted participants and those with other coexisting viral diseases. We considered any of the various pharmacological interventions compared with placebo or each other. **Data collection and analysis:** We used standard methodological procedures expected by Cochrane. We calculated the odds ratio (OR) and rate ratio with 95% confidence intervals (CI) using both fixed-effect and random-effects models based on the available-participant analysis with Review Manager 5. We assessed risk of bias according to Cochrane, controlled risk of random errors with Trial Sequential Analysis, and assessed the quality of the evidence using GRADE.

Main results: We identified 10 randomised clinical trials with 488 randomised participants that met our inclusion criteria. All the trials were at high risk of bias in one or more domains. Overall, the evidence for all the outcomes was very low quality evidence. Nine trials (467 participants) provided information for one or more outcomes. Three trials (99 participants) compared interferon-alpha versus no intervention. Three trials (90 participants) compared interferon-beta versus no intervention. One trial (21 participants) compared pegylated interferon-alpha versus no intervention, but it did not provide any data for analysis. One trial (41 participants) compared MTH-68/B vaccine versus no intervention. Two trials (237 participants) compared pegylated interferon-alpha versus pegylated interferon-alpha plus ribavirin. None of the trials compared direct-acting antivirals versus placebo or other interventions. The mean or median follow-up period in the trials ranged from six to 36 months.
There was no short-term mortality (less than one year) in any group in any trial except for one trial where one participant died in the pegylated interferon-alpha plus ribavirin group (1/95: 1.1%). In the trials that reported follow-up beyond one year, there were no further deaths. The number of serious adverse events was higher with pegylated interferon-alpha plus ribavirin than with pegylated interferon-alpha (rate ratio 2.74, 95% CI 1.40 to 5.33; participants = 237; trials = 2; I^2 = 0%). The proportion of people with any adverse events was higher with interferon-alpha and interferon-beta compared with no intervention (OR 203.00, 95% CI 9.01 to 4574.81; participants = 33; trials = 1 and OR 27.88, 95% CI 1.48 to 526.12; participants = 40; trials = 1). None of the trials reported health-related quality of life, liver transplantation, decompensated liver disease, cirrhosis, or hepatocellular carcinoma. The proportion of people with chronic HCV infection as indicated by the lack of sustained virological response was lower in the interferon-alpha group versus no intervention (OR 0.27, 95% CI 0.09 to 0.76; participants = 99; trials = 3; I^2 = 0%). The differences between the groups were imprecise or not estimable (because neither group had any events) for all the remaining comparisons.
Four of the 10 trials (40%) received financial or other assistance from pharmaceutical companies who would benefit from the findings of the research; the source of funding was not available in five trials (50%), and one trial (10%) was funded by a hospital.
Authors' conclusions: Very low quality evidence suggests that interferon-alpha may decrease the incidence of chronic HCV infection as measured by sustained virological response. However, the clinical impact such as improvement in health-related quality of life, reduction in cirrhosis, decompensated liver disease, and liver transplantation has not been reported. It is also not clear whether this finding is applicable in the current clinical setting dominated by the use of pegylated interferons and direct-acting antivirals, although we found no evidence to support that pegylated interferons or ribavirin or both are effective in people with acute HCV infection. We could find no randomised trials comparing direct-acting antivirals with placebo or other interventions for acute HCV infection. There is significant uncertainty in the benefits and harms of the interventions, and high-quality randomised clinical trials are required.
Kalafateli M, Buzzetti E, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Pharmacological interventions for acute hepatitis C infection. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD011644. DOI: 10.1002/14651858.CD011644.pub3.

Irritable bowel syndrome (IBS)

13. Limited, low-quality data suggest fecal transplant is ineffective for patients with IBS

Clinical question: Does fecal transplantation improve symptoms in patients with irritable bowel syndrome?
Study design: Meta-analysis (randomized controlled trials) **Setting:** Various (meta-analysis)
Synopsis: These authors searched several databases to identify randomized trials that compared fecal transplant with placebo treatment in patients older than 16 years with IBS. Additionally, they hand-searched bibliographies from conferences and the reference lists of included studies. Two authors independently assessed studies for inclusion and evaluated the methodologic quality of the included studies. The authors don't describe how they reconciled disagreements. They ultimately included only 4 studies with 254 patients. Two of the studies have not yet been fully published and were only available in abstract form. All used the ROME III criteria for the diagnosis of IBS. One study administered the transplant via colonoscopy, one via nasojejunal tube, and 2 via oral capsules. One of the studies was at low risk of bias and the other 3 were of uncertain risk of bias (my hunch is that these 3 were not low risk!). Two studies reported global improvement in the placebo-treated patients and 2 reported global improvement in the transplant-treated patients; pooling resulted in no net effect. The 2 studies that showed global deterioration used oral capsules (number needed to treat to harm = 3; 95% CI 2 - 10). Two studies reported an improvement in quality of life during the first 12 weeks following treatment, but not afterward. The authors did a bunch of subgroup analyses, but they seem rather silly given the small number of patients and the uncertain study quality.
Bottom line: The available research on the effectiveness of fecal transplantation in patients with irritable bowel syndrome (IBS) is limited in number and quality, and the net effect suggests it is not effective. Stay tuned for more and better studies.
Xu D, Chen VL, Steiner CA, et al. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol 2019;114(7):1043-1050.

14. Rifaximin and some probiotics lessen symptoms in patients with IBS

Clinical question: Do treatments aimed at changing the gastrointestinal biome affect symptoms of irritable bowel syndrome?
Study design: Systematic review **Setting:** Various (meta-analysis)
Synopsis: These researchers combed 3 databases, including the Cochrane Controlled Trials Register, to identify randomized controlled trials of prebiotic treatment, probiotic treatment, and rifaximin in adults with IBS. They included studies in any language and also searched for reference lists of retrieved studies. Two reviewers independently abstracted study data and evaluated the studies for bias. Prebiotic treatment with fructooligosaccharides showed no benefit as compared with placebo in 2 of the 3 studies, though the studies were at risk of bias and were likely underpowered. Probiotic treatment using the combination of Bifidobacterium longum, B. bifidum, B. lactis, Lactobacillus acidophilus, L. rhamnosus, and Streptococcus thermophiles (LacClean Gold) was more effective than placebo in 2 studies of 130 patients, improving global symptoms and abdominal pain. Two small studies of 78 patients showed a 7-strain combination (3 Bifidobacterium, 3 Lactobacillus, and 1 Streptococcus) to be more effective than placebo. The combination of L. paracasei ssp paracasei F19, L. acidophilus La5, and B. lactis Bb12 (3 studies, 269 patients) found no benefit over placebo. Five studies of 1805 patients with IBS and diarrhea found benefit with the nonabsorbed antibiotic rifaximin.
Bottom line: When it comes to the bacterial community in the gastrointestinal (GI) tract, we can suppress the population with antibiotics, encourage new neighbors with probiotics, or selectively feed good citizens with prebiotics. In this systematic review of

studies of colon urban planning, overall suppression of GI flora with the antibiotic rifaximin (Xifaxan) was effective for irritable bowel syndrome (IBS) with diarrhea. Some, but not all probiotics have proved effectiveness to decrease overall symptoms and abdominal pain. Prebiotics have not been shown to be effective in small studies.
Ford AC, Harris LA, Lacy BE, Quigley EM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment Pharmacol Ther 2018;48(10):1044-1060.

15. Minesapride = placebo to reduce constipation in patients with IBS with predominant constipation

Clinical question: Is minesapride (Ibsrela®) more effective than placebo to increase spontaneous bowel movements in patients with irritable bowel syndrome with predominant constipation?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (specialty)
Synopsis: These investigators enrolled 411 patients (86% women) with a history of severe IBS-C (Rome IV) with an average daily abdominal pain score of 5.6 out of a possible 10, an average of less than 3 spontaneous bowel movements per week, and an average of 0.34 complete spontaneous bowel movements per week. After 2 weeks of placebo treatment to establish a baseline, the patients were randomized, allocation concealment uncertain, to receive placebo or minesapride 10 mg, 20 mg, or 40 mg daily for 3 months. The primary endpoint, analyzed by modified intention-to-treat, was an increase in one or more complete spontaneous bowel movements plus an improvement of 30% or more from baseline in the weekly average worst abdominal pain score. This outcome was not different with treatment or placebo after 6 or 12 weeks of treatment (13.6% - 19.2%), regardless of dose. More than 94% of patients completed the study. Analysis was by modified intention to treat.
Bottom line: Minesapride, an investigational treatment for irritable bowel syndrome with predominant constipation (IBS-C), is no more effective than placebo in affecting the composite outcome of reducing abdominal pain and increasing spontaneous bowel movements in patients with severe symptoms.
Hamatani T, Fukudo S, Nakada Y, Inada H, Kazumori K, Miwa H. Randomised clinical trial: minesapride vs placebo for irritable bowel syndrome with predominant constipation. Aliment Pharmacol Ther 2020;52(3):430-441.

16. Antidepressants decrease symptoms of IBS; benefit of psychological therapies is less clear

Clinical question: Are antidepressants and psychological therapies effective in decreasing symptoms in patients with IBS?
Study design: Meta-analysis (randomized controlled trials) **Setting:** Various (meta-analysis)
Synopsis: These authors systematically searched several databases, a clinical trial registry, and abstracts of conference proceedings to identify randomized trials of antidepressants or psychological therapies in the treatment of adults with IBS. The trials of antidepressants had to include a placebo comparator, while the psychological therapy trials could include placebo, symptom monitoring, or usual care. Two of the authors independently evaluated papers for inclusion and assessed the risk of bias. They resolved disagreements by consensus, and ultimately included 53 trials. The studies ranged in size from 15 to 172 patients; 17 studies compared antidepressants with placebo, 35 compared psychological therapies with control therapy or usual care, and 1 compared both psychological therapy and antidepressants with placebo. The main outcome was a dichotomous assessment of any improvement in global IBS symptoms or abdominal pain. The studies that evaluated drugs included 1127 patients. Only 4 were at low risk of bias. Overall, 57% of actively treated patients had global improvement compared with 34% of placebo-treated patients (number needed to treat [NNT] = 5; 95% CI 4 - 6). Additionally, 52% of actively treated patients had improvement in abdominal pain compared with 27% of placebo-treated patients (NNT = 4; 3 - 7). There was statistically significant heterogeneity among these outcomes. Most of the improvement in abdominal pain was from tricyclic antidepressants. Only 8 studies reported on adverse events, finding that 36% of actively treated patients had adverse events compared with 21% of placebo-treated patients (number needed to treat to harm = 9; 5 - 21). The studies that evaluated psychological therapies included 2487 patients and assessed several treatments including cognitive behavioral therapy (CBT), relaxation therapy, hypnotherapy, Internet-based CBT, psychotherapy, mindfulness-based meditation, stress management, or various combinations of these. Other than a lack of masking, the authors report these studies were generally at low risk of bias. Overall, 48% of patients receiving psychological therapies had global improvement compared with 24% of control patients (NNT = 5; 4 - 5). Among individual therapies, the following were effective: CBT (NNT = 4; 3 - 9), relaxation (NNT = 6; 3 - 60), multicomponent therapy (NNT = 4; 3 - 7), hypnotherapy (NNT = 5; 3.5 - 10), and dynamic psychotherapy (NNT = 4; 2 - 20). Overall, the authors found significant heterogeneity as well as evidence for publication bias among the studies, so the final word is not out!
Bottom line: Antidepressants, particularly tricyclic antidepressants, are effective in improving symptoms in patients with irritable bowel syndrome (IBS), but at the risk of adverse events. The data on psychological therapies, while promising, are not as convincing.
Ford AC, Lacy BE, Harris LA, Quigley EMM, Moayyedi P. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol 2019;114(1):21-39.

17. American College of Gastroenterology guideline on managing persons with IBS

Clinical question: How should clinicians manage irritable bowel syndrome?
Study design: Practice guideline **Funding source:** Self-funded or unfunded
Synopsis: The American College of Gastroenterology convened a panel of "experts" (no explicit description of how they were selected or in which domains they were "expert"; many of whom declared conflicts of interest) who formulated 25 key statements that the guideline was to assess. Each statement was evaluated by a broad search of multiple databases and the Cochrane Clinical Trials register. Although the authors prioritized randomized trials with at least 10 participants that lasted at least 4 weeks, they used other study designs where appropriate. A trained methodologist helped assess the quality of the evidence for each of the 25 statements, a few of which are summarized as follows. Based on a meta-analysis of persons presenting with symptoms of IBS, which found that about 3% of these patients had positive test results for celiac disease, the panel strongly recommends serologic testing for celiac disease (e.g., anti-endomysial antibodies, tissue transglutaminase antibodies). Additionally, in patients with alarm symptoms of inflammatory bowel disease, the panel strongly recommends testing with C-reactive protein or fecal calprotectin (moderate-quality evidence) or fecal lactoferrin (low-quality evidence). In the absence of alarm symptoms, the panel conditionally recommends against routine colonoscopy in those younger than 45 years. The consensus of the panel (i.e., with no data to support) was to categorize

patients with IBS into subgroups based on stool consistency. In the absence of a suggestive history, the consensus was against testing for food allergies or food intolerances. Additionally, the panel's consensus recommendation was to perform anorectal physiology testing in patients with symptoms or findings suggestive of pelvic floor disorders or in those with refractory constipation. Based on limited data, the panel made a conditional recommendation for an initial trial of a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet. They also strongly recommend, based on a meta-analysis of 15 randomized trials, the use of soluble (but not insoluble) fiber to treat IBS symptoms. They conditionally recommend against the use of antispasmodics (limited data and lots of adverse effects), probiotics, polyethylene glycol, bile acid sequestrants, and fecal transplant. The panel conditionally recommended peppermint oil but made strong recommendations for the use of tricyclic antidepressants, chloride channel activators (lubiprostone is the only one they mention; ~$300 US per month; red alert for possible conflict of interest), guanylate cyclase activators (linaclotide or plecanatide, each ~$500 US per month), and rifamaxin ($2800 US per month). The authors made a conditional recommendation for the use of mixed opioid agonists/antagonists (specifically, eluxadoline: $1400 US per month) and for gut-directed psychotherapy. This is a pretty long guideline and it contains a few useful resources, such as the Rome criteria, Bristol Stool Form Scale, tools to aid identification of pelvic floor disorders, and tricyclic dosing for IBS. Consider getting a copy, especially if you want to see all 25 recommendations!
Bottom line: The American College of Gastroenterology recommends that patients with suspected irritable bowel syndrome (IBS) undergo serologic testing (to rule out celiac disease) and selected additional testing based on the clinical circumstances. Additionally, they recommend a trial of a low FODMAP diet. Although they emphasize several new and expensive medications to treat symptoms, they also recommend using tricyclic antidepressants and recommend against using antispasmodic agents.
Lacy BE, Pimentel M, Brenner DM, et al. ACG clinical guideline: management of irritable bowel syndrome. Am J Gastroenterol 2021;116(1):17-44.

18. British Society of Gastroenterology guideline on managing persons with IBS

Clinical question: What is the best way to manage irritable bowel syndrome?
Study design: Practice guideline **Funding source:** Foundation
Synopsis: These guidelines from the British Society of Gastroenterology were created by a multidisciplinary panel that included primary care physicians, psychologists, dietitians, and gastroenterologists. Treatment recommendations were based on systematic reviews, and all other recommendations were based on a comprehensive review of the literature. There are dozens of recommendations; I'll outline the highlights. The guidelines advocate a pragmatic definition of irritable bowel syndrome (IBS) as at least 6 months of abdominal pain or discomfort, in association with altered bowel habits, in the absence of alarm signs or symptoms. Initial evaluation in primary care should include a complete blood count, C-reactive protein or sedimentation rate, and serology for celiac disease. For patients younger than 45 years who present with diarrhea, order a fecal calprotectin test to rule out inflammatory bowel disease. Screen for colorectal cancer in accordance with national guidelines; colonoscopy is only recommended for patients with alarm signs and symptoms or who are at increased risk for microscopic colitis (female, at least 50 years old, with comorbid autoimmune disease; weight loss; diarrhea for less than 12 months; or severe, nocturnal, or watery diarrhea). Consider testing for bile acid diarrhea in patients with nocturnal diarrhea or prior cholecystectomy. The guidelines recommend against testing for pancreatic insufficiency, small intestinal bacterial overgrowth, or carbohydrate intolerance if the symptoms are typical for IBS. First-line treatment recommendations include exercise and gradually increasing doses of soluble fiber (eg, ispaghula) but not insoluble fiber (eg, wheat bran). Consider probiotics, although the guideline doesn't recommend a specific species or dose. Consider loperamide for diarrheal symptoms; antispasmodics and peppermint oil for global symptoms, as well as abdominal pain and cramping; and polyethylene glycol for constipation. (Note that a recent POEM found no benefit to peppermint oil in a well-designed trial). Second-line drugs in primary care include tricyclic antidepressants and selective serotonin reuptake inhibitors. Other drug classes, such as medications targeting 5-HT-3 and 5-HT-4 receptors, should be prescribed after evaluation by a gastroenterologist.
Bottom line: This high-quality evidence-based guideline provides sound advice for the evaluation and management of persons with IBS in primary care.
Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut 2021;70(7):1214-1240.

Bottom Lines:

- Fecal calprotectin is accurate in identifying kids with inflammatory bowel disease
- POCUS is accurate in diagnosing appendicitis
- Surgery vs. Abx for appendicitis: tradeoffs provide an opportunity for shared decision-making
- Screen adolescents and adults for hepatitis C
- In adults with suspected IBS, testing should be limited to serologic testing for celiac disease and to C-reactive protein or fecal calprotectin in pts with IBD alarm symptoms
- Treat persons with IBS with soluble fiber followed by FODMAP, loperamide for diarrhea, PEG for constipation and secondary treatment with TCAs, lubiprostone, linaclotide or plecanatide, rifamaxin

Exercise Update — Gary Ferenchick MD

Learning objectives | Understand and apply:

- Primary care interventions are assoc with higher uptake of exercise
- On average one lives longer with exercise and more low risk lifestyle factors
- Adopting more “low risk lifestyle factors”, including exercise, during midlife is assoc with longer life
- Subsymptom threshold aerobic exercise treatment hastens concussion recovery
- Return-to-play (RTP) is safe among athletes recovering from COVID

The New England J of Medicine has started a series of articles on "The Evidence for Exercise in Medicine", the first of which was published in Feb 2022. (The Evidence for Exercise in Medicine — A New Review Series. NEJM Evid 2022; 1 (3). Among the points made by the authors included the following:

- Although the incidence of most noncommunicable diseases increases with chronologic age, *chronic disease is not an inevitable consequence of aging*.
- Most chronic diseases are partly *attributable to decreasing levels of physical activity and increasing levels of sedentarism*, along with increased consumption of highly processed foods and other environmental changes.
- Physical inactivity is a potent risk factor for disease.
- Total physical activity in the United States declined by 32% from 1965 to 2009.

As you sit here quietly listening to this talk, your energy expenditure is ~ 1.2 kcal/minute. If you are an average 70-kg human, then in the next hour you will expend 84 calories doing this “activity”. Stated another way, doing this same “activity” you are consuming ~ 3.5 milliliters of oxygen/kg of body weight/min. This number is also referred to as **1 MET**, and METS are a common way to quantify exercise.

The following table groups several kinds of physical activity into Moderate Intensity (3.5 to 7 kcal/minute OR 3.0 to 6.0 METs) and Vigorous Activity (> 7 kcal/minute OR > 6.0 METs). The US Department of Health and Human Services recommends 150 minutes/week of moderate-intensity (~ **22**/**minutes per day**) exercise, or 75 minutes per weeks of vigorous-intensity exercise for all US adults.

The following tables identify several common moderate- and vigorous-intensity exercises.

Examples of moderate- to vigorous-intensity exercises	
Moderate-intensity aerobic exercise	Vigorous-intensity aerobic exercise
Stationary cycling – moderate effort	Stationary cycling – vigorous effort
Hiking	Jogging/running
Water aerobics	Step aerobics
Yoga	Stair climber at a fast pace
Tennis - doubles	Tennis -singles
Golf - walking	Handball/racquetball/squash

Table 4. Definitions and Examples of Different Intensities of Physical Activity

Intensity	METs	Examples
Sedentary behavior*	1–1.5	Sitting, reclining, or lying; watching television
Light	1.6–2.9	Walking slowly, cooking, light housework
Moderate	3.0–5.9	Brisk walking (2.4–4 mph), biking (5–9 mph), ballroom dancing, active yoga, recreational swimming
Vigorous	≥6	Jogging/running, biking (≥10 mph), singles tennis, swimming laps

**Sedentary behavior* is defined as any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture. Standing is a sedentary activity in that it involves ≤1.5 METs, but it is not considered a component of sedentary behavior.

MET indicates metabolic equivalent; and mph, miles per hour.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140:e596–e646

Centers for Disease Control and Prevention | Measuring Physical Activity Intensity

Moderate Intensity

- The talk test is a simple way to measure relative intensity. In general, if you're doing moderate-intensity activity, you can talk but not sing during the activity.

Vigorous Intensity

- In general, if you're doing vigorous-intensity activity, you will not be able to say more than a few words without pausing for a breath.

#1. Primary care interventions improve uptake of MVPA

Objective To examine the effectiveness of physical activity interventions delivered or prompted by primary care health professionals for increasing moderate to vigorous intensity physical activity (MVPA) in adult patients.
Design Systematic review and meta-analysis of randomised controlled trials.
Data sources Databases (Medline and Medline in progress, Embase, PsycINFO, CINAHL, SPORTDiscus, Sports Medicine and Education Index, ASSIA, PEDro, Bibliomap, Science Citation Index, Conference Proceedings Citation Index), trial registries (Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, TRoPHI), and grey literature (OpenGrey) sources were searched (from inception to September 2020).
Eligibility criteria for selecting studies Randomised controlled trials of aerobic based physical activity interventions delivered or prompted by health professionals in primary care with a usual care control group or another control group that did not involve physical activity.
Study selection and analysis Two independent reviewers screened the search results, extracted data from eligible trials and assessed the risk of bias using the Cochrane risk of bias tool (version 2). Inverse variance meta-analyses using random effects models examined the primary outcome of difference between the groups in MVPA (min/week) from baseline to final follow-up. The odds of meeting the guidelines for MVPA at follow-up were also analysed.
Results 14 566 unique reports were identified and 46 randomised controlled trials with a range of follow-ups (3-60 months) were included in the meta-analysis (n=16 198 participants). Physical activity interventions delivered or prompted by health professionals in primary care increased MVPA by 14 min/week (95% confidence interval 4.2 to 24.6, P=0.006). Heterogeneity was substantial (I2=91%, P<0.001). Limiting analyses to trials that used a device to measure physical activity showed no significant group difference in MVPA (mean difference 4.1 min/week, 95% confidence interval −1.7 to 9.9, P=0.17; I2=56%, P=0.008). Trials that used self-report measures showed that intervention participants achieved 24 min/week more MVPA than controls (95% confidence interval 6.3 to 41.8, P=0.008; I2=72%, P<0.001). Additionally, interventions increased the odds of patients meeting guidelines for MVPA by 33% (95% confidence interval 1.17 to 1.50, P<0.001; I2=25%, P=0.11) versus controls. 14 of 46 studies were at high risk of bias but sensitivity analyses excluding these studies did not alter the results.

Conclusions Physical activity interventions delivered or prompted by health professionals in primary care appear effective at increasing participation in self-reported MVPA. Such interventions should be considered for routine implementation to increase levels of physical activity and improve health outcomes in the population.
Reference: Effectiveness of physical activity interventions delivered or prompted by health professionals in primary care settings: systematic review and meta-analysis of randomised controlled trials. BMJ 2022;376:e068465

Your chance of living longer is greater if you exercise

#2. < 150 min/week of moderate-to-vigorous-intensity physical activity (MVPA) associated with 22% mortality benefit

BACKGROUND: The health benefits of 150 min a week of moderate-to-vigorous-intensity physical activity (MVPA) in older adults, as currently recommended, are well established, but the suggested dose in older adults is often not reached.
OBJECTIVES: We aimed to determine whether a lower dose of MVPA was effective in reducing mortality, in participants older than 60 years.
METHODS: The PubMed and Embase databases were searched from inception to February 2015. Only prospective cohorts were included. Risk ratios of death were established into four doses based on weekly Metabolic Equivalent of Task (MET)-minutes, defined as inactive (reference), low (1-499), medium (500-999) or high (≥1000). Data were pooled and analysed through a random effects model using comprehensive meta-analysis software.
RESULTS: Of the 835 reports screened, nine cohort studies remained, totalling 122 417 participants, with a mean follow-up of 9.8±2.7 years and 18 122 reported deaths (14.8%). A low dose of MVPA resulted in a 22% reduction in mortality risk (RR=0.78 (95% CI 0.71 to 0.87) p<0.0001). MVPA beyond this threshold brought further benefits, reaching a 28% reduction in all-cause mortality in older adults who followed the current recommendations (RR=0.72 (95% CI 0.65 to 0.80) p<0.0001) and a 35% reduction beyond 1000 MET-min per week (RR=0.65 (95% CI 0.61 to 0.70) p<0.0001).
CONCLUSIONS: A dose of MVPA below current recommendations reduced mortality by 22% in older adults. A further increase in physical activity dose improved these benefits in a linear fashion. Older adults should be encouraged to include even low doses of MVPA in their daily lives.
REFERENCE: Hupin D et al. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥60 years: a systematic review and meta-analysis. Br J Sports Med. 2015 Oct;49(19):1262-7. PMID: 26238869

#3. In addition to more exercise, sitting less is assoc with longer life(on average)

OBJECTIVE: To examine the dose-response associations between accelerometer assessed total physical activity, different intensities of physical activity, and sedentary time and all-cause mortality.
DESIGN: Systematic review and harmonised meta-analysis.
DATA SOURCES: PubMed, PsycINFO, Embase, Web of Science, Sport Discus from inception to 31 July 2018.
ELIGIBILITY CRITERIA: Prospective cohort studies assessing physical activity and sedentary time by accelerometry and associations with all cause mortality and reported effect estimates as hazard ratios, odds ratios, or relative risks with 95% confidence intervals.
DATA EXTRACTION AND ANALYSIS: Guidelines for meta-analyses and systematic reviews for observational studies and PRISMA guidelines were followed. Two authors independently screened the titles and abstracts. One author performed a full text review and another extracted the data. Two authors independently assessed the risk of bias. Individual level participant data were harmonised and analysed at study level. Data on physical activity were categorised by quarters at study level, and study specific associations with all cause mortality were analysed using Cox proportional hazards regression analyses. Study specific results were summarised using random effects meta-analysis.
MAIN OUTCOME MEASURE: All-cause mortality.
RESULTS: 39 studies were retrieved for full text review; 10 were eligible for inclusion, three were excluded owing to harmonisation challenges (eg, wrist placement of the accelerometer), and one study did not participate. Two additional studies with unpublished mortality data were also included. Thus, individual level data from eight studies (n=36 383; mean age 62.6 years; 72.8% women), with median follow-up of 5.8 years (range 3.0-14.5 years) and 2149 (5.9%) deaths were analysed. Any physical activity, regardless of intensity, was associated with lower risk of mortality, with a non-linear dose-response. Hazards ratios for mortality were 1.00 (referent) in the first quarter (least active), 0.48 (95% confidence interval 0.43 to 0.54) in the second quarter, 0.34 (0.26 to 0.45) in the third quarter, and 0.27 (0.23 to 0.32) in the fourth quarter (most active). Corresponding hazards ratios for light physical activity were 1.00, 0.60 (0.54 to 0.68), 0.44 (0.38 to 0.51), and 0.38 (0.28 to 0.51), and for moderate-to-vigorous physical activity were 1.00, 0.64 (0.55 to 0.74), 0.55 (0.40 to 0.74), and 0.52 (0.43 to 0.61). For sedentary time, hazards ratios were 1.00 (referent; least sedentary), 1.28 (1.09 to 1.51), 1.71 (1.36 to 2.15), and 2.63 (1.94 to 3.56).
CONCLUSION: Higher levels of total physical activity, at any intensity, and less time spent sedentary, are associated with substantially reduced risk for premature mortality, with evidence of a non-linear dose-response pattern in middle aged and older adults.
REFERENCE: Ekelund U et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all-cause mortality: systematic review and harmonised meta-analysis. BMJ. 2019 Aug 21;366:l4570

#4. Your chances are better even if you exercise a little bit

OBJECTIVE: To investigate the association of running participation and the dose of running with the risk of all-cause, cardiovascular and cancer mortality.
DESIGN: Systematic review and meta-analysis.

DATA SOURCES: Journal articles, conference papers and doctoral theses indexed in Academic Search Ultimate, CINAHL, Health Source: Nursing/Academic Edition, MasterFILE Complete, Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, PsycINFO, PubMed/MEDLINE, Scopus, SPORTDiscus and Web of Science.
ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Prospective cohort studies on the association between running or jogging participation and the risk of all-cause, cardiovascular and/or cancer mortality in a non-clinical population of adults were included.
RESULTS: Fourteen studies from six prospective cohorts with a pooled sample of 232 149 participants were included. In total, 25 951 deaths were recorded during 5.5-35 year follow-ups. Our meta-analysis showed that running participation is associated with 27%, 30% and 23% lower risk of all-cause (pooled adjusted hazard ratio (HR)=0.73; 95% confidence interval (CI) 0.68 to 0.79), cardiovascular (HR=0.70; 95% CI 0.49 to 0.98) and cancer (HR=0.77; 95% CI 0.68 to 0.87) mortality, respectively, compared with no running. A meta-regression analysis showed no significant dose-response trends for weekly frequency, weekly duration, pace and the total volume of running.
CONCLUSION: Increased rates of participation in running, regardless of its dose, would probably lead to substantial improvements in population health and longevity. Any amount of running, even just once a week, is better than no running, but higher doses of running may not necessarily be associated with greater mortality benefits.
REFERENCE: Pedisic Z et al. Is running associated with a lower risk of all-cause, cardiovascular and cancer mortality, and is the more the better A systematic review and meta-analysis. Br J Sports Med British Journal of Sports Medicine Published Online First: 04 November 2019

"Bite Size Snacks of Exercise" NY Times Jan 23, 2019

#5. But a higher % of time in vigorous physical activity (VPA) is assoc with more benefit.

Importance: It is unclear whether, for the same amount of total physical activity, a higher proportion of vigorous physical activity (VPA) to total physical activity is associated with a greater reduction in mortality.
Objective: To examine the association of the proportion of VPA to total physical activity (defined as moderate to vigorous physical activity [MVPA]) with all-cause mortality, cardiovascular disease mortality, and cancer mortality.
Design, Setting, and Participants: This cohort study included 403 681 adults from the National Health Interview Survey 1997-2013 who provided data on self-reported physical activity and were linked to the National Death Index records through December 31, 2015. Statistical analysis was performed from May 15, 2018, to August 15, 2020.
Exposures: Proportion of VPA to total physical activity among participants performing any MVPA.
Main Outcomes and Measures: All-cause mortality, cardiovascular disease mortality, and cancer mortality. Cox proportional hazards regression models were performed to estimate hazard ratios (HRs) and 95% CIs, adjusted for sociodemographic characteristics, lifestyle risk factors, and total physical activity.
Results: Among the 403 681 individuals (225 569 women [51.7%]; mean [SD] age, 42.8 [16.3] years) in the study, during a median 10.1 years (interquartile range, 5.4-14.6 years) of follow-up (407.3 million person-years), 36 861 deaths occurred. Mutually adjusted models considering the recommendations of moderate physical activity (MPA; 150-299 vs 0 minutes per week) and VPA (≥75-149 vs 0 minutes per week) showed similar associations for all-cause mortality (MPA: HR, 0.83; 95% CI, 0.80-0.87; and VPA: HR, 0.80; 95% CI, 0.76-0.84) and cardiovascular disease mortality (MPA: HR, 0.75; 95% CI, 0.68-0.83; and VPA: HR, 0.79; 95% CI, 0.70-0.91). For the same contrasts, VPA (HR, 0.89; 95% CI, 0.80-0.99) showed a stronger inverse association with cancer mortality compared with MPA (HR, 0.94; 95% CI, 0.86-1.02). Among participants performing any MVPA, a higher proportion of VPA to total physical activity was associated with lower all-cause mortality but not with cardiovascular disease and cancer mortality. For instance, compared with participants with 0% of VPA (no vigorous activity), participants performing greater than 50% to 75% of VPA to total physical activity had a 17% lower all-cause mortality (hazard ratio, 0.83; 95% CI, 0.78-0.88), independent of total MVPA. The inverse association between proportion of VPA to total physical activity and all-cause mortality was consistent across sociodemographic characteristics, lifestyle risk factors, and chronic conditions at baseline.
Conclusions and Relevance: This study suggests that, for the same volume of MVPA, a higher proportion of VPA to total physical activity was associated with lower all-cause mortality. Clinicians and public health interventions should recommend 150 minutes or more per week of MVPA but also advise on the potential benefits associated with VPA to maximize population health.
Reference: Association of Physical Activity Intensity With Mortality A National Cohort Study of 403 681 US Adults. JAMA Intern Med. 2021;181(2):203-211.

Counting Steps

#6 More steps associated with lower mortality

Importance: It is unclear whether the number of steps per day and the intensity of stepping are associated with lower mortality.
Objective: Describe the dose-response relationship between step count and intensity and mortality.
Design, Setting, and Participants: Representative sample of US adults aged at least 40 years in the National Health and Nutrition Examination Survey who wore an accelerometer for up to 7 days (from 2003-2006). Mortality was ascertained through December 2015.
Exposures: Accelerometer-measured number of steps per day and 3 step intensity measures (extended bout cadence, peak 30-minute cadence, and peak 1-minute cadence [steps/min]). Accelerometer data were based on measurements obtained during a 7-day period at baseline.
Main Outcomes and Measures: The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular disease (CVD) and cancer mortality. Hazard ratios (HRs), mortality rates, and 95% CIs were estimated using cubic splines and quartile classifications adjusting for age; sex; race/ethnicity; education; diet; smoking status; body mass index; self-reported health; mobility limitations; and diagnoses of diabetes, stroke, heart disease, heart failure, cancer, chronic bronchitis, and emphysema.

Results: A total of 4840 participants (mean age, 56.8 years; 2435 [54%] women; 1732 [36%] individuals with obesity) wore accelerometers for a mean of 5.7 days for a mean of 14.4 hours per day. The mean number of steps per day was 9124. There were 1165 deaths over a mean 10.1 years of follow-up, including 406 CVD and 283 cancer deaths. The unadjusted incidence density for all-cause mortality was 76.7 per 1000 person-years (419 deaths) for the 655 individuals who took less than 4000 steps per day; 21.4 per 1000 person-years (488 deaths) for the 1727 individuals who took 4000 to 7999 steps per day; 6.9 per 1000 person-years (176 deaths) for the 1539 individuals who took 8000 to 11 999 steps per day; and 4.8 per 1000 person-years (82 deaths) for the 919 individuals who took at least 12 000 steps per day. Compared with taking 4000 steps per day, taking 8000 steps per day was associated with significantly lower all-cause mortality (HR, 0.49 [95% CI, 0.44-0.55]), as was taking 12 000 steps per day (HR, 0.35 [95% CI, 0.28-0.45]). Unadjusted incidence density for all-cause mortality by peak 30 cadence was 32.9 per 1000 person-years (406 deaths) for the 1080 individuals who took 18.5 to 56.0 steps per minute; 12.6 per 1000 person-years (207 deaths) for the 1153 individuals who took 56.1 to 69.2 steps per minute; 6.8 per 1000 person-years (124 deaths) for the 1074 individuals who took 69.3 to 82.8 steps per minute; and 5.3 per 1000 person-years (108 deaths) for the 1037 individuals who took 82.9 to 149.5 steps per minute. Greater step intensity was not significantly associated with lower mortality after adjustment for total steps per day (eg, highest vs lowest quartile of peak 30 cadence: HR, 0.90 [95% CI, 0.65-1.27]; *P* value for trend = .34).
Conclusions and Relevance: Based on a representative sample of US adults, a greater number of daily steps was significantly associated with lower all-cause mortality. There was no significant association between step intensity and mortality after adjusting for total steps per day.
Reference: Association of Daily Step Count and Step Intensity With Mortality Among US Adults. JAMA. 2020;323(12):1151-1160.

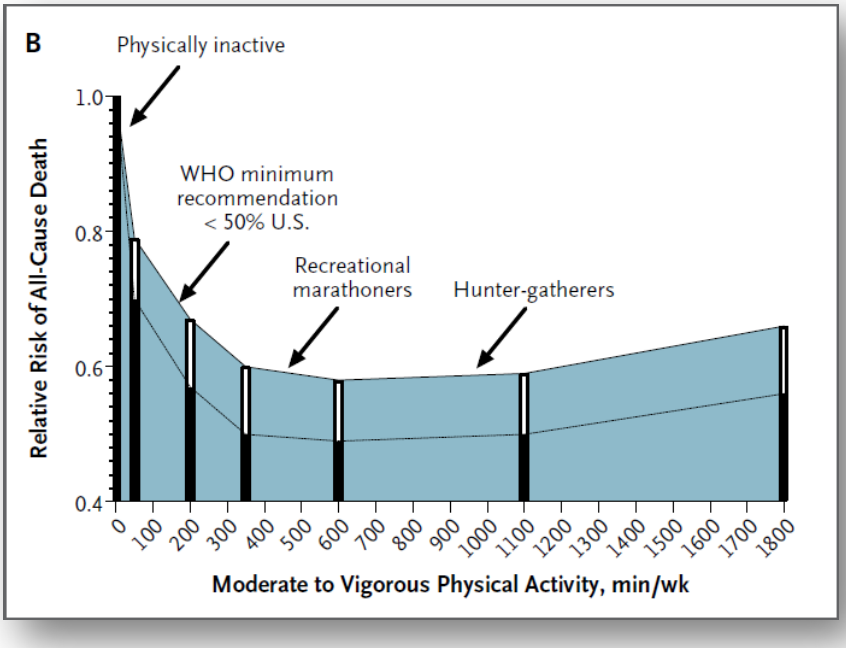
#7. And 7000 Steps per Day is the "sweet spot"

Importance: Steps per day is a meaningful metric for physical activity promotion in clinical and population settings. To guide promotion strategies of step goals, it is important to understand the association of steps with clinical end points, including mortality.
Objective: To estimate the association of steps per day with premature (age 41-65 years) all-cause mortality among Black and White men and women.
Design, Setting, and Participants: This prospective cohort study was part of the Coronary Artery Risk Development in Young Adults (CARDIA) study. Participants were aged 38 to 50 years and wore an accelerometer from 2005 to 2006. Participants were followed for a mean (SD) of 10.8 (0.9) years. Data were analyzed in 2020 and 2021.
Exposure: Daily steps volume, classified as low (<7000 steps/d), moderate (7000-9999 steps/d), and high (≥10 000 steps/d) and stepping intensity, classified as peak 30-minute stepping rate and time spent at 100 steps/min or more.
Main Outcomes and Measures: All-cause mortality.
Results: A total of 2110 participants from the CARDIA study were included, with a mean (SD) age of 45.2 (3.6) years, 1205 (57.1%) women, 888 (42.1%) Black participants, and a median (interquartile range [IQR]) of 9146 (7307-11 162) steps/d. During 22 845 person years of follow-up, 72 participants (3.4%) died. Using multivariable adjusted Cox proportional hazards models, compared with participants in the low step group, there was significantly lower risk of mortality in the moderate (hazard ratio [HR], 0.28 [95% CI, 0.15-0.54]; risk difference [RD], 53 [95% CI, 27-78] events per 1000 people) and high (HR, 0.45 [95% CI, 0.25-0.81]; RD, 41 [95% CI, 15-68] events per 1000 people) step groups. Compared with the low step group, moderate/high step rate was associated with reduced risk of mortality in Black participants (HR, 0.30 [95% CI, 0.14-0.63]) and in White participants (HR, 0.37 [95% CI, 0.17-0.81]). Similarly, compared with the low step group, moderate/high step rate was associated with reduce risk of mortality in women (HR, 0.28 [95% CI, 0.12-0.63]) and men (HR, 0.42 [95% CI, 0.20-0.88]). There was no significant association between peak 30-minute intensity (lowest vs highest tertile: HR, 0.98 [95% CI, 0.54-1.77]) or time at 100 steps/min or more (lowest vs highest tertile: HR, 1.38 [95% CI, 0.73-2.61]) with risk of mortality.
Conclusions and Relevance: This cohort study found that among Black and White men and women in middle adulthood, participants who took approximately 7000 steps/d or more experienced lower mortality rates compared with participants taking fewer than 7000 steps/d. There was no association of step intensity with mortality.
Reference: Steps per Day and All-Cause Mortality in Middle-aged Adults in the Coronary Artery Risk Development in Young Adults Study. JAMA Netw Open. 2021;4(9):e2124516

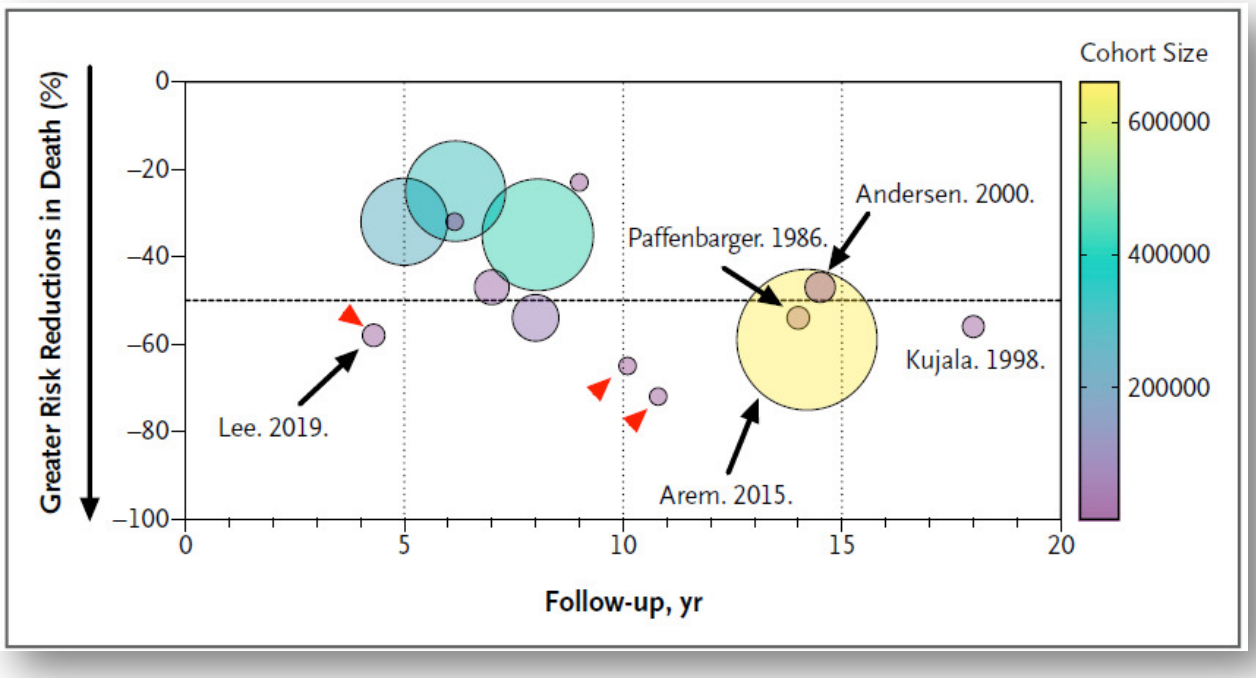
#8 110,000 deaths can potentially be prevented annually with 10 minutes of exercise daily

Objective: In this study, we used accelerometer measurements (1) to examine the association of physical activity and mortality in a population-based sample of US adults and (2) to estimate the number of deaths prevented annually with modest increases in moderate-to-vigorous physical activity intensity (MVPA).
Methods: This cohort study was approved by the National Center for Health Statistics Ethics Review Board. This study used data from the National Health and Nutrition Examination Survey (NHANES), and written informed consent was obtained for all NHANES participants. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Race and ethnicity was determined by self-report and classified using preferred terminology from the National Center for Health Statistics as Mexican American, non-Hispanic Black, non-Hispanic White, or other. Race and ethnicity was included in this study to better characterize the US population. For this study, we evaluated 4840 of 6355 adults aged 40 to 85 years or older with accelerometer data. Mortality follow-up was completed via National Death Index linkage through December 31, 2015. We estimated MVPA by summing accelerometer minutes at or above an established cutpoint4 and creating 8 physical activity categories (0-19, 20-39, 40-59, 60-79, 80-99, 100-119, 120-139, or ≥140 minutes per day).
The number of deaths per year prevented with increased physical activity was estimated as the adjusted population attributable fraction (PAF)5 multiplied by the US population annual number of deaths for 2003 (for individuals aged 40-84 years).
Results: This analysis included 4840 participants. Of these, 2435 (53%) were women, 993 (10.4%) were non-Hispanic Black, and 887 (5.1%) were Mexican American (Table). A total of 1165 deaths occurred during a mean (SEM) follow-up of 10.1 (0.1) years. Adjusted hazard ratios changed from 0.69 to 0.28 across increasing activity categories (vs 0-19 minutes per day). Hazard ratios used to generate the PAFs for the 8 activity categories were as follows: 1.00 (reference) for 0 to 19 (548 [7.9%]), 0.69 (95% CI, 0.55-0.85) for 20 to 39

(616 [10.0%]), 0.51 (95% CI, 0.42-0.63) for 40 to 59 (635 [11.8%]), 0.40 (95% CI, 0.29-0.55) for 60 to 79 (614 [12.7%]), 0.34 (95% CI, 0.25-0.47) for 80-99 (633 [14.4%]), 0.32 (95% CI, 0.21-0.48) for 100 to 119 (508 [12.1%]), 0.30 (95% CI, 0.19-0.48) for 120-139 (384 [9.3%]), and 0.28 (95% CI, 0.18-0.42) for 140 or more (902 [21.7%]) minutes per day. The number of participants with frailty or needing special equipment was 280 (49.4%) for 0 to 19, 164 (26.3%) for 20 to 39, 94 (12.4%) for 40 to 59, 66 (9.5%) for 60 to 79, 42 (5.1%) for 80 to 99, 31 (4.7%) for 100 to 119, 20 (2.9%) for 120 to 139, and 35 (2.7%) for 140 or more minutes per day.
Increasing MVPA by 10, 20, or 30 minutes per day was associated with a 6.9%, 13.0%, and 16.9% decrease in the number of deaths per year, respectively. Adding 10 minutes per day of physical activity resulted in an estimated 111 174 preventable deaths per year (95% CI, 79 594-142 754), with greater benefits associated with the addition of more physical activity (209 459 preventable deaths [95% CI, 146 299-272 619] for 20 minutes and 272 297 preventable deaths [95% CI, 177 557-367 037] for 30 minutes) (Figure).
The PAFs indicate that the addition of 10 minutes per day of MVPA was associated with the prevention of 8.0% (95% CI, 6.0-10.0) of total deaths per year among men, 5.9% (95% CI, 2.0-9.8) among women, 4.8% (95% CI, 0.0-10.7) among Mexican American individuals, 6.1% (95% CI, 2.2-10.0) among non-Hispanic Black individuals, and 7.3% (95% CI, 5.3-9.3) among non-Hispanic White individuals.
Discussion: In this cohort study, we estimated that approximately 110 000 deaths per year could be prevented if US adults aged 40 to 85 years or older increased their MVPA by a small amount (ie, 10 minutes per day). Similar benefits were observed for men and women and for Mexican American, non-Hispanic Black, and non-Hispanic White adults. To our knowledge, this is the first study to estimate the number of preventable deaths through physical activity using accelerometer-based measurements among US adults while recognizing that increasing activity may not be possible for everyone. However, 1 week of monitoring may not reflect changes in activity over time, and the observational study design limits the direct determination of causality.
Conclusions: These findings support implementing evidence-based strategies to improve physical activity for adults and potentially reduce deaths in the US.
Reference: Estimated Number of Deaths Prevented Through Increased Physical Activity Among US Adults. JAMA Intern Med. 2022;182(3):349-352



- Large-scale studies show that 150 minutes of moderate to vigorous physical activity per week reduces the relative mortality rate by approximately 33%, and additional doses yield further but comparatively less benefit.
- "... numerous observational data sets linking health outcomes to habitual physical activity are strongly suggestive of a causal effect."



(The Evidence for Exercise in Medicine — A New Review Series. NEJM Evid 2022; 1 (3).

In the following 2 abstracts five lifestyle factors adhered to in midlife were positively associated with 8 – 11 years of added life expectancy; these were (drum roll please!):

- Never smoking
- BMI 18.5 – 24.9
- Exercise > 30 minutes daily
- Moderate ETOH intake (5-15 g/day women, 5 – 30 gm /d men
- Higher dietary quality

These are very similar to the ACC/AHA's Life's Essential 8

- Physical activity
- Eat better
- Don't smoke
- Sleep
- Body weight
- Control cholesterol
- Reduce blood sugar
- Manage BP

#9. More "low risk lifestyle factors" in midlife is assoc with longer health span (by a lot!)

Objective: To examine how a healthy lifestyle is related to life expectancy that is free from major chronic diseases.
Design: Prospective cohort study.
Setting and participants: The Nurses' Health Study (1980-2014; n=73 196) and the Health Professionals Follow-Up Study (1986-2014; n=38 366).
Main exposures: Five low risk lifestyle factors: never smoking, body mass index 18.5-24.9, moderate to vigorous physical activity (≥30 minutes/day), moderate alcohol intake (women: 5-15 g/day; men 5-30 g/day), and a higher diet quality score (upper 40%).
Main outcome: Life expectancy free of diabetes, cardiovascular diseases, and cancer.
Results: The life expectancy free of diabetes, cardiovascular diseases, and cancer at age 50 was 23.7 years (95% confidence interval 22.6 to 24.7) for women who adopted no low risk lifestyle factors, in contrast to 34.4 years (33.1 to 35.5) for women who adopted four

or five low risk factors. At age 50, the life expectancy free of any of these chronic diseases was 23.5 (22.3 to 24.7) years among men who adopted no low risk lifestyle factors and 31.1 (29.5 to 32.5) years in men who adopted four or five low risk lifestyle factors. For current male smokers who smoked heavily (≥15 cigarettes/day) or obese men and women (body mass index ≥30), their disease-free life expectancies accounted for the lowest proportion (≤75%) of total life expectancy at age 50.
Conclusion: Adherence to a healthy lifestyle at mid-life is associated with a longer life expectancy free of major chronic diseases.
Reference: Yanping Li et al. Healthy Lifestyle and Life Expectancy Free of Cancer, Cardiovascular Disease, and Type 2 Diabetes: Prospective Cohort Study. BMJ 2020; 368

#10. Ditto

Background: Americans have a shorter life expectancy compared with residents of almost all other high-income countries. We aim to estimate the impact of lifestyle factors on premature mortality and life expectancy in the US population.
Methods: Using data from the Nurses' Health Study (1980-2014; n=78 865) and the Health Professionals Follow-up Study (1986-2014, n=44 354), we defined 5 low-risk lifestyle factors as never smoking, body mass index of 18.5 to 24.9 kg/m2, ≥30 min/d of moderate to vigorous physical activity, moderate alcohol intake, and a high diet quality score (upper 40%), and estimated hazard ratios for the association of total lifestyle score (0-5 scale) with mortality. We used data from the NHANES (National Health and Nutrition Examination Surveys; 2013-2014) to estimate the distribution of the lifestyle score and the US Centers for Disease Control and Prevention WONDER database to derive the age-specific death rates of Americans. We applied the life table method to estimate life expectancy by levels of the lifestyle score.
Results: During up to 34 years of follow-up, we documented 42 167 deaths. The multivariable-adjusted hazard ratios for mortality in adults with 5 compared with zero low-risk factors were 0.26 (95% confidence interval [CI], 0.22-0.31) for all-cause mortality, 0.35 (95% CI, 0.27-0.45) for cancer mortality, and 0.18 (95% CI, 0.12-0.26) for cardiovascular disease mortality. The population-attributable risk of nonadherence to 5 low-risk factors was 60.7% (95% CI, 53.6-66.7) for all-cause mortality, 51.7% (95% CI, 37.1-62.9) for cancer mortality, and 71.7% (95% CI, 58.1-81.0) for cardiovascular disease mortality. We estimated that the life expectancy at age 50 years was 29.0 years (95% CI, 28.3-29.8) for women and 25.5 years (95% CI, 24.7-26.2) for men who adopted zero low-risk lifestyle factors. In contrast, for those who adopted all 5 low-risk factors, we projected a life expectancy at age 50 years of 43.1 years (95% CI, 41.3-44.9) for women and 37.6 years (95% CI, 35.8-39.4) for men. The projected life expectancy at age 50 years was on average 14.0 years (95% CI, 11.8-16.2) longer among female Americans with 5 low-risk factors compared with those with zero low-risk factors; for men, the difference was 12.2 years (95% CI, 10.1-14.2).
Conclusions: Adopting a healthy lifestyle could substantially reduce premature mortality and prolong life expectancy in US adults.
Reference: Li Y et al. Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. Circulation 2018;138:345

Recovery & Return to Play Post Concussion / COVID

#11. In adolescents with concussion, subsymptom aerobic exercise hastens recovery

IMPORTANCE: Sport-related concussion (SRC) is a significant public health problem without an effective treatment.
OBJECTIVE: To assess the effectiveness of subsymptom threshold aerobic exercise vs a placebo-like stretching program prescribed to adolescents in the acute phase of recovery from SRC.
DESIGN, SETTING, AND PARTICIPANTS: This multicenter prospective randomized clinical trial was conducted at university concussion centers. Male and female adolescent athletes (age 13-18 years) presenting within 10 days of SRC were randomly assigned to aerobic exercise or a placebo-like stretching regimen.
INTERVENTIONS: After systematic determination of treadmill exercise tolerance on the first visit, participants were randomly assigned to a progressive subsymptom threshold aerobic exercise or a progressive placebo-like stretching program (that would not substantially elevate heart rate). Both forms of exercise were performed approximately 20 minutes per day, and participants reported daily symptoms and compliance with exercise prescription via a website.
MAIN OUTCOMES AND MEASURES: Days from injury to recovery; recovery was defined as being asymptomatic, having recovery confirmed through an assessment by a physician blinded to treatment group, and returning to normal exercise tolerance on treadmill testing. Participants were also classified as having normal (<30 days) or delayed (=30 days) recovery.
RESULTS: A total of 103 participants were included (aerobic exercise: n=52; 24 female [46%]; stretching, n=51; 24 female [47%]). Participants in the aerobic exercise group were seen a mean (SD) of 4.9 (2.2) days after the SRC, and those in the stretching group were seen a mean (SD) of 4.8 (2.4) days after the SRC. There were no differences in age, sex, previous concussions, time from injury, initial symptom severity score, or initial exercise treadmill test and physical examination results. Aerobic exercise participants recovered in a median of 13 (interquartile range [IQR], 10-18.5) days, whereas stretching participants recovered in 17 (IQR, 13-23) days (P=.009 by Mann-Whitney test). There was a nonsignificant lower incidence of delayed recovery in the aerobic exercise group (2 participants [4%] in the aerobic group vs 7 [14%] in the placebo group; P=.08).
CONCLUSIONS AND RELEVANCE: This is, to our knowledge, the first RCT to show that individualized subsymptom threshold aerobic exercise treatment prescribed to adolescents with concussion symptoms during the first week after SRC speeds recovery and may reduce the incidence of delayed recovery.
REFERENCE: Leddy Jj et al. Early Subthreshold Aerobic Exercise for Sport-Related Concussion: A Randomized Clinical Trial. JAMA Pediatr. 2019 Apr 1;173(4):319-325.

#12: Ditto

Background: Sport-related concussion is a public health problem, particularly in adolescents. Quality of life is reduced in adolescents with persistent post-concussive symptoms (symptoms >28 days). We replicated a previous randomised controlled trial to validate the safety, efficacy, and generalisability of, and objective adherence to, prescribed early targeted heart rate subsymptom threshold aerobic

exercise compared with placebo-like stretching exercise for adolescent recovery from sport-related concussion and for reducing the risk of persistent post-concussive symptoms.
Methods: This randomised controlled trial was done at three community and hospital-affiliated sports medicine concussion centres in the USA. Male and female adolescent athletes (aged 13–18 years) presenting within 10 days of sport-related concussion were randomly assigned to individualised subsymptom threshold aerobic or stretching exercise at least 20 min daily, for up to 4 weeks after injury. Exercise adherence and intensity were measured by heart rate monitors. The primary outcome was clinical recovery (ie, return to baseline symptoms, normal exercise tolerance, and a normal physical examination) within the 4-week intervention period, and development of persistent post-concussive symptoms beyond 28 days after injury. This study is registered with ClinicalTrials.gov, NCT02959216.
Findings: Between Aug 1, 2018, and March 31, 2020, 118 adolescents were recruited (61 were randomly assigned to the aerobic exercise group and 57 to the stretching exercise group) and included in the intention-to-treat analysis. On survival analysis, controlling for sex, site, and mean daily exercise time, patients assigned to aerobic exercise were more likely to recover within 4 weeks after injury compared with those assigned to stretching exercise, with a 48% reduced risk of persistent post-concussive symptoms (hazard ratio for stretching vs aerobic exercise of 0·52 [95% CI 0·28–0·97], p=0·039). No adverse events were reported.
Interpretation: This multicentre study found that early treatment with subsymptom threshold aerobic exercise safely speeds recovery from sport-related concussion and reduces the risk for persistent post-concussive symptoms, an important result given the impact of delayed recovery on adolescent quality of life. Adherence was good and there were no adverse events from this non-pharmacological treatment. These results suggest that physicians should not only permit, but consider prescribing, early subsymptom threshold physical activity to adolescents as treatment for sport-related concussion and to reduce the risk of persistent post-concussive symptoms.
Reference: Early targeted heart rate aerobic exercise versus placebo stretching for sport-related concussion in adolescents: a randomised controlled trial. The Lancet Child & Adolescent Health. Volume 5, Issue 11, November 2021, Pages 792-799

Light aerobic exercise reduced duration of recovery and persistent postconcussive symptoms in adolescents.

#13: Return to play (RTP) is safe post-COVID

Importance: The major North American professional sports leagues were among the first to return to full-scale sport activity during the coronavirus disease 2019 (COVID-19) pandemic. Given the unknown incidence of adverse cardiac sequelae after COVID-19 infection in athletes, these leagues implemented a conservative return-to-play (RTP) cardiac testing program aligned with American College of Cardiology recommendations for all athletes testing positive for COVID-19.
Objective: To assess the prevalence of detectable inflammatory heart disease in professional athletes with prior COVID-19 infection, using current RTP screening recommendations.
Design, Setting, and Participants: This cross-sectional study reviewed RTP cardiac testing performed between May and October 2020 on professional athletes who had tested positive for COVID-19. The professional sports leagues (Major League Soccer, Major League Baseball, National Hockey League, National Football League, and the men's and women's National Basketball Association) implemented mandatory cardiac screening requirements for all players who had tested positive for COVID-19 prior to resumption of team-organized sports activities.
Exposures: Troponin testing, electrocardiography (ECG), and resting echocardiography were performed after a positive COVID-19 test result. Interleague, deidentified cardiac data were pooled for collective analysis. Those with abnormal screening test results were referred for additional testing, including cardiac magnetic resonance imaging and/or stress echocardiography.
Main Outcomes and Measures: The prevalence of abnormal RTP test results potentially representing COVID-19–associated cardiac injury, and results and outcomes of additional testing generated by the initial screening process.
Results: The study included 789 professional athletes (mean [SD] age, 25 [3] years; 777 men [98.5%]). A total of 460 athletes (58.3%) had prior symptomatic COVID-19 illness, and 329 (41.7%) were asymptomatic or paucisymptomatic (minimally symptomatic). Testing was performed a mean (SD) of 19 (17) days (range, 3-156 days) after a positive test result. Abnormal screening results were identified in 30 athletes (3.8%; troponin, 6 athletes [0.8%]; ECG, 10 athletes [1.3%]; echocardiography, 20 athletes [2.5%]), necessitating additional testing; 5 athletes (0.6%) ultimately had cardiac magnetic resonance imaging findings suggesting inflammatory heart disease (myocarditis, 3; pericarditis, 2) that resulted in restriction from play. No adverse cardiac events occurred in athletes who underwent cardiac screening and resumed professional sport participation.
Conclusions and Relevance: This study provides large-scale data assessing the prevalence of relevant COVID-19–associated cardiac pathology with implementation of current RTP screening recommendations. While long-term follow-up is ongoing, few cases of inflammatory heart disease have been detected, and a safe return to professional sports activity has thus far been achieved.
Reference: Prevalence of Inflammatory Heart Disease Among Professional Athletes With Prior COVID-19 Infection Who Received Systematic Return-to-Play Cardiac Screening. JAMA Cardiol. 2021;6(7):745-752.

Conclusions

- Primary care interventions improve uptake of moderate-to-vigorous activity
- MVPA associated with improved mortality
- More daily steps assoc with more lifespan & ~ 7000 seems to be the "sweet spot"
- Adopting more "low risk lifestyle factors" midlife is assoc with longer life
- Sub-symptom threshold aerobic exercise hastens concussion recovery
- Return-to-play (RTP) is safe among most athletes recovering from COVID

Dementia and end of life care 2022 Henry C. Barry, MD, MS

Objectives: At the end of this session, the participant will be able to:

- describe approaches to identifying persons who are near end of life
- describe the natural history of mild cognitive impairment
- describe recent approaches to managing persons with dementia

End of Life

1. Surprise Question for identifying primary care patients who will die in the next year

Clinical question: Which risk assessment is better at identifying patients who might benefit from palliative care, the Surprise Question or the Supportive and Palliative Care Indicators Tool (SPICT)?
Study design: Cohort (prospective) **Funding source:** Government
Synopsis: The SQ asks: "Would I be surprised if this patient died in the next 12 months?" These authors argue that palliative care should be consulted if the answer is no, which seems reasonable. The SPICT is a list of indicators, such as a diagnosis of advanced cancer, dementia, or frailty, that are suggestive of a need for palliative care. The authors test the accuracy of each risk assessment in 2 Dutch primary care practices (N = 3640 patients). The general practitioners used clinical intuition to identify 57 patients in one practice for whom they would answer no to the SQ, and only 10 such patients in the other practice. The SPICT was encoded to automatically search the electronic health record and it identified 501 potential candidates. The identified cases were reviewed by the general practitioners, who agreed with the assessment of a potential need for palliative care for 88 patients and 13 patients, respectively, in the 2 practices. Cancer, dementia, and heart failure were the most common relevant comorbidities in selected patients; 79% of the patients identified by the SQ and 69% by the SPICT were 80 years or older. After one year, 36 had died. The authors looked at who had died in each of the groups of identified patients. For the SQ, sensitivity was 50% and specificity 99% (positive likelihood ratio [LR+] 50; negative likelihood ratio [LR−] 0.50); for the SPICT, sensitivity was 58% and specificity 98% (LR+ 29; LR− 0.43). The positive predictive value was 27% for the SQ in this primary care population where overall mortality was 1%. When 10 patients whose deaths could not have been easily predicted were excluded, sensitivity improved to 69% for the SQ and 81% for the SPICT. Because of the burden of going through 501 patient records to narrow down the selection, general practitioners liked the SQ better. The SQ asks: "Would I be surprised if this patient died in the next 12 months?" These authors argue that palliative care should be consulted if the answer is no, which seems reasonable. The SPICT is a list of indicators, such as a diagnosis of advanced cancer, dementia, or frailty, that are suggestive of a need for palliative care. The authors test the accuracy of each risk assessment in 2 Dutch primary care practices (N = 3640 patients). The general practitioners used clinical intuition to identify 57 patients in one practice for whom they would answer no to the SQ, and only 10 such patients in the other practice. The SPICT was encoded to automatically search the electronic health record and it identified 501 potential candidates. The identified cases were reviewed by the general practitioners, who agreed with the assessment of a potential need for palliative care for 88 patients and 13 patients, respectively, in the 2 practices. Cancer, dementia, and heart failure were the most common relevant comorbidities in selected patients; 79% of the patients identified by the SQ and 69% by the SPICT were 80 years or older. After one year, the authors looked at who had died in each of the groups of identified patients. For the SQ, sensitivity was 50% and specificity 99% (positive likelihood ratio [LR+] 50; negative likelihood ratio [LR−] 0.50); for the SPICT, sensitivity was 58% and specificity 98% (LR+ 29; LR− 0.43). The positive predictive value was 27% for the SQ in this primary care population where overall mortality was 1%. When 10 patients whose deaths could not have been easily predicted were excluded, sensitivity improved to 69% for the SQ and 81% for the SPICT. Because of the burden of going through 501 patient records to narrow down the selection, general practitioners liked the SQ better.
Bottom line: The Surprise Question (SQ; "Would I be surprised if this patient died in the next 12 months?") has a good positive predictive value in primary care (33%) and should prompt consideration of a palliative care referral. The authors of this study preferred the SPICT because it is more sensitive (58% vs 50%), but it is more time-consuming to implement.
van Wijmen MP, Schweitzer BP, Pasman HR, Onwuteaka-Philipsen BD. Identifying patients who could benefit from palliative care by making use of the general practice information system: the Surprise Question versus the SPICT. Fam Pract 2020;37(5)641-647.

2. Lower costs and healthcare utilization with hospital care at home

Clinical question: Can hospitalization at home reduce health care costs?
Study design: Randomized controlled trial (nonblinded)
Synopsis: This study took place at an academic medical center and a community hospital in the United States. Eligible patients were adults who presented to the emergency department who required admission for one of the following conditions: infection, heart failure, chronic obstructive pulmonary disease, asthma, chronic kidney disease requiring diuresis, diabetic complications, acute gout, hypertensive urgency, previously diagnosed atrial fibrillation with rapid ventricular rate, anticoagulation needs, or patients at end-of-life desiring medical management only. Of the 248 eligible patients, 157 were excluded, primarily because the patient or family declined to be in the study. Using concealed allocation, the investigators randomized the remaining patients to home care (n = 43) or usual care in the hospital (n = 48). The home care patients received 1 daily visit from an internist and 2 daily visits from a nurse, with additional visits as needed 24 hours a day. Specialty consultation was accessed via telemedicine. Respiratory therapies, intravenous medications, radiology, and blood diagnostic tests could be provided at home, and other services such as physical and occupational therapy were available as needed. All patients had continuous vitals, telemetry, and monitoring for movement and falls via a skin patch device. Patients in the 2 groups were chronically ill, frail, and elderly (median age = 80 years in the home group and 72 years in hospital group). Overall, the adjusted mean cost of an acute care episode, which included the costs for nonphysician labor, supplies, medications, and diagnostic tests, was 38% lower in the home group (95% CI 24% - 49%; P < .001). Home patients had fewer imaging studies (14% vs 44%), laboratory tests (3 vs 15), and consultations (2% vs 31%). They spent less time each day sedentary (12% vs. 23%) or lying down

(18% vs. 55%). "Length of stay" was slightly longer for home patients (4.5 days vs 3.8 days), but home patients were less likely to be re-admitted within 30 days (7% vs 23%). Both groups reported high satisfaction with their care.
Bottom line: Home hospitalization can reduce the cost of care and healthcare utilization for an acute illness episode. Findings from this study, however, are less generalizable as the study took place at only 2 sites with a small group of physicians and highly selected patients. Nevertheless, the results are promising; more research is needed to explore the possibility of hospital-level care at home.
Levine DM, Ouchi K, Blanchfield B, et al. Hospital-level care at home for acutely ill adults. Ann Intern Med 2020;172(2):77-85.

3. Online module promotes advance directives documentation

Clinical question: Can an online module help older patients complete advance directives?
Study design: Randomized controlled trial (single-blinded) **Setting:** Outpatient (primary care)
Synopsis: These investigators enrolled 986 English-speaking or Spanish-speaking (45%) primary care patients, mean age 63.3 years, with 2 or more chronic or serious illnesses. Approximately 40% of the group had low health literacy. The patients were randomized, concealed allocation unknown, to receive an advance directive form to take home, or to receive the same form and computer access to review the PREPARE online module. Patients in both groups were asked about advance care planning at a subsequent visit. Within 15 months of the initial exposure to the interventions, 43% of patients who reviewed the online module had documented advance directives compared with 33.1% in the paper-only group (number needed to treat = 10). Results were significant in both English-speaking and Spanish-speaking patients. This is a proof-of-concept study and the results might not be the same if patients were asked to go home and review the online module on their own computers. As they say in advertisements, your results may differ.
Bottom line: An online module called PREPARE (https://prepareforyourcare.org/welcome) helps patients make choices for their end-of-life care and gives them the option of creating an advance directive to share with their clinicians. It might be a good resource for computer-savvy patients. The tool is available in English and Spanish. Another online resource is Five Wishes (https://fivewishes.org/), and is available in 27 languages.
Sudore RL, Schillinger D, Katen MT, et al. Engaging diverse English- and Spanish-speaking older adults in advance care planning. The PREPARE randomized clinical trial. JAMA Intern Med 2018;178(12):1616-1625.

4. Advance care planning increases advance directives and surrogate decision-maker assignment

Clinical question: Does advance care planning lead to increased completion of advance directives and selection of surrogate decision makers among frail elders?
Study design: Randomized controlled trial (nonblinded) **Funding source:** Foundation
Synopsis: These researchers conducted a cluster randomized trial of facilitated advance care planning education or usual care among modestly frail elders living in residential care homes or receiving home care nearby. The education intervention included trained facilitators and educational materials and tools intended to identify the patients' goals, values, and preferences regarding their health care and to assist in identifying a surrogate decision maker in the event of noncompetence. In addition to assigning an "activation score" (not all that important), the researchers assessed whether the patient had documented their advance care preferences and had selected a surrogate decision maker. The researchers included 16 clusters that contributed 201 patients (between 1 and 53 patients per cluster). The patients in each group were in their mid-80s and, unsurprisingly, most were female. The intervention patients were more likely to receive home-based care (61%) and to have completed high school (65%) than the control patients (49% and 40%, respectively). At the end of 1 year, 93% of the intervention group had completed an advance directive compared with 34% of control patients (number needed to treat [NNT] = 2; 95% CI 2 - 3). Additionally, 94% of the intervention participants had identified a surrogate decision maker compared with 67% of the control patients (NNT= 4; 3 - 6). Unfortunately, the consultation sessions took an average of 2 hours, including travel time, to complete.
Bottom line: In this study, an intensive advance care planning intervention dramatically increased the completion of advance directives and the identification of surrogate decision makers.
Overbeek A, Korfage IJ, Jabbarian LJ, et al. Advance care planning in frail older adults: a cluster randomized controlled trial. J Am Geriatr Soc 2018;66(6):1089-1095.

5. Patients' preferred place of death: if asked patients are willing to consider their preferences

BACKGROUND: end-of-life care is not always in line with end-of-life preferences, so patients do not always die at their preferred place of death (PPD). This study aims to identify factors associated with patients' PPD and changes in PPD. **METHODS:** we prospectively collected data on PPD at four time points within 6 months from 230 acutely hospitalised older patients who were part of the control group in a stepped-wedge randomised controlled trial. Associations between patient characteristics and preferences were calculated using multivariable (multinomial) logistic regression analysis. **RESULTS:** the mean age of participants was 80.7 years. 47.8% of the patients had no PPD at hospital admission. Patients previously admitted to hospital preferred to die at home (home versus no preference: odds ratio [OR] 2.38, 95% confidence interval [CI] 1.15-4.92; home versus healthcare facility: OR 3.25, 95% CI 1.15-9.16). Patients with more chronic diseases preferred the healthcare facility as their PPD (healthcare facility versus no preference: OR 1.33, 95% CI 1.09-1.61; healthcare facility versus home: OR 1.21, 95% CI 1.00-1.47). 32 of 65 patients changed their preference during follow-up, and most of these had no PPD at hospital admission (home versus no preference: OR 0.005, 95% CI </=0.001-0.095) and poorer self-rated well-being (OR 1.82, 95% CI 1.07-3.08). **CONCLUSIONS:** almost half of the patients had no PPD at baseline. Previous hospital admission, having more chronic diseases and living alone are associated with having a PPD. Introducing PPD could make older people aware of PPD and facilitate optimal palliative care.
van Doorne I, van Rijn M, Dofferhoff SM, Willems DL, Buurman BM. Patients' preferred place of death: patients are willing to consider their preferences, but someone has to ask them. Age Ageing. 2021;50(6):2004-2011.

6. Hospital-based specialist palliative care for adults with advanced illness and their caregivers

Background: Serious illness is often characterised by physical/psychological problems, family support needs, and high healthcare resource use. Hospital-based specialist palliative care (HSPC) has developed to assist in better meeting the needs of patients and their families and potentially reducing hospital care expenditure. There is a need for clarity on the effectiveness and optimal models of HSPC, given that most people still die in hospital and also to allocate scarce resources judiciously. **Objectives:** To assess the effectiveness and cost-effectiveness of HSPC compared to usual care for adults with advanced illness (hereafter patients) and their unpaid caregivers/families.
Search methods: We searched CENTRAL, CDSR, DARE and HTA database via the Cochrane Library; MEDLINE; Embase; CINAHL; PsycINFO; CareSearch; National Health Service Economic Evaluation Database (NHS EED) and two trial registers to August 2019, together with checking of reference lists and relevant systematic reviews, citation searching and contact with experts to identify additional studies. **Selection criteria:** We included randomised controlled trials (RCTs) evaluating the impact of HSPC on outcomes for patients or their unpaid caregivers/families, or both. HSPC was defined as specialist palliative care delivered by a palliative care team that is based in a hospital providing holistic care, co-ordination by a multidisciplinary team, and collaboration between HSPC providers and generalists. HSPC was provided to patients while they were admitted as inpatients to acute care hospitals, outpatients or patients receiving care from hospital outreach teams at home. The comparator was usual care, defined as inpatient or outpatient hospital care without specialist palliative care input at the point of entry into the study, community care or hospice care provided outside of the hospital setting. **Data collection and analysis:** We used standard methodological procedures expected by Cochrane. We assessed risk of bias and extracted data. To account for use of different scales across studies, we calculated standardised mean differences (SMDs) with 95% confidence intervals (CIs) for continuous data. We used an inverse variance random-effects model. For binary data, we calculated odds ratio (ORs) with 95% CIs. We assessed the evidence using GRADE and created a 'Summary of findings' table. Our primary outcomes were patient health-related quality of life (HRQoL) and symptom burden (a collection of two or more symptoms). Key secondary outcomes were pain, depression, satisfaction with care, achieving preferred place of death, mortality/survival, unpaid caregiver burden, and cost-effectiveness. Qualitative data was analysed where available.
Main results: We identified 42 RCTs involving 7779 participants (6678 patients and 1101 caregivers/family members). Twenty-one studies were with cancer populations, 14 were with non-cancer populations (of which six were with heart failure patients), and seven with mixed cancer and non-cancer populations (mixed diagnoses).
HSPC was offered in different ways and included the following models: ward-based, inpatient consult, outpatient, hospital-at-home or hospital outreach, and service provision across multiple settings which included hospital. For our main analyses, we pooled data from studies reporting adjusted endpoint values. Forty studies had a high risk of bias in at least one domain.
Compared with usual care, HSPC improved patient HRQoL with a small effect size of 0.26 SMD over usual care (95% CI 0.15 to 0.37; I2 = 3%, 10 studies, 1344 participants, low-quality evidence, higher scores indicate better patient HRQoL). HSPC also improved other person-centred outcomes. It reduced patient symptom burden with a small effect size of -0.26 SMD over usual care (95% CI -0.41 to -0.12; I2 = 0%, 6 studies, 761 participants, very low-quality evidence, lower scores indicate lower symptom burden). HSPC improved patient satisfaction with care with a small effect size of 0.36 SMD over usual care (95% CI 0.41 to 0.57; I2 = 0%, 2 studies, 337 participants, low-quality evidence, higher scores indicate better patient satisfaction with care). Using home death as a proxy measure for achieving patient's preferred place of death, patients were more likely to die at home with HSPC compared to usual care (OR 1.63, 95% CI 1.23 to 2.16; I2 = 0%, 7 studies, 861 participants, low-quality evidence). Data on pain (4 studies, 525 participants) showed no evidence of a difference between HSPC and usual care (SMD -0.16, 95% CI -0.33 to 0.01; I2 = 0%, very low-quality evidence). Eight studies (N = 1252 participants) reported on adverse events and very low-quality evidence did not demonstrate an effect of HSPC on serious harms. Two studies (170 participants) presented data on caregiver burden and both found no evidence of effect of HSPC (very low-quality evidence). We included 13 economic studies (2103 participants). Overall, the evidence on cost-effectiveness of HSPC compared to usual care was inconsistent among the four full economic studies. Other studies that used only partial economic analysis and those that presented more limited resource use and cost information also had inconsistent results (very low-quality evidence).
Quality of the evidence: The quality of the evidence assessed using GRADE was very low to low, downgraded due to a high risk of bias, inconsistency and imprecision.
Authors' conclusions: Very low- to low-quality evidence suggests that when compared to usual care, HSPC may offer small benefits for several person-centred outcomes including patient HRQoL, symptom burden and patient satisfaction with care, while also increasing the chances of patients dying in their preferred place (measured by home death). While we found no evidence that HSPC causes serious harms, the evidence was insufficient to draw strong conclusions. Although these are only small effect sizes, they may be clinically relevant at an advanced stage of disease with limited prognosis, and are person-centred outcomes important to many patients and families. More well conducted studies are needed to study populations with non-malignant diseases and mixed diagnoses, ward-based models of HSPC, 24 hours access (out-of-hours care) as part of HSPC, pain, achieving patient preferred place of care, patient satisfaction with care, caregiver outcomes (satisfaction with care, burden, depression, anxiety, grief, quality of life), and cost-effectiveness of HSPC. In addition, research is needed to provide validated person-centred outcomes to be used across studies and populations.
Bajwah S, Oluyase AO, Yi D, Gao W, Evans CJ, Grande G, Todd C, Costantini M, Murtagh FE, Higginson IJ. The effectiveness and cost-effectiveness of hospital-based specialist palliative care for adults with advanced illness and their caregivers. Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD012780. DOI: 10.1002/14651858.CD012780.pub2.

7. Subcutaneous scopolamine butylbromide reduces the death rattle in dying patients (SILENCE)

Clinical Question: Can prophylactic scopolamine butylbromide reduce the incidence of the death rattle?
Study Design: Randomized controlled trial (double-blinded) **Funding:** Government **Setting:** Inpatient (ward only)
Synopsis: In dying patients, the noisy breathing due to the presence of mucus in the upper respiratory tract is known as the death rattle. Clinicians often use anticholinergics, which decrease mucus production, to diminish the death rattle as it can be distressing to family and caregivers. However, there is no great evidence to support their use. In this study from the Netherlands, investigators enrolled patients who'd been admitted to inpatient hospice and had entered the dying phase. Those with respiratory infections were excluded. Study patients were randomized to receive prophylactic scopolamine butylbromide 20 mg (n = 79) or matching placebo (n =

78) administered via a subcutaneous catheter 4 times daily. The study medication was continued until death or until the occurrence of a death rattle that was audible at the foot of the patient bed at 2 time points 6 hours apart. Overall, fewer patients in the scopolamine group than in the placebo group developed the death rattle (13% vs 27%; P = .02). There were no significant differences between the 2 groups in drug-related adverse events, including restlessness, dry mouth, or urinary retention. Despite randomization, there was a higher incidence of lung cancer, chronic obstructive pulmonary disease, and smoking history in the placebo group. Although this imbalance may have potentially contributed to more mucus production in the placebo group, a post-hoc analysis showed that placebo-treated patients with these conditions had a lower occurrence of death rattle than the entire placebo group.
Bottom Line: Scopolamine butylbromide, administered subcutaneously to dying patients, can reduce the incidence of the death rattle. Although this may be comforting to family and caregivers, it is unclear whether the death rattle is distressing to patients themselves. Of note, this medication is only available outside the United States. Moreover, it is distinct from the transdermal scopolamine that is used in the United States in that it does not cross the blood-brain barrier and is given in much higher doses.
Van Esch H, Van Zuylen L, Geijteman ECT, et al. Effect of prophylactic subcutaneous scopolamine butylbromide on death rattle in patients at the end of life: The SILENCE Randomized Clinical Trial. JAMA 2021;326(13):1268-1276.

Mild Cognitive Impairment

This is a syndrome that causes great fear and apprehension among older persons. While the American Academy of Neurology guideline doesn't have much about therapy, it provides reassurance about its variable course.

8. AAN guideline for patients with mild cognitive impairment

Clinical question: How should clinicians manage patients with mild cognitive impairment (MCI)?
Study design: Practice guideline **Funding source:** Foundation
Synopsis: This guideline development panel was convened by the American Academy of Neurology (AAN). The panel used a systematic review of the literature to address 4 broad areas important to managing patients with MCI: prevalence, prognosis, pharmacologic management, and nonpharmacologic management. Overall, 62 studies informed the panel's recommendations. One of the challenges the panel faced is the variability in definition of MCI. Their best guess is that MCI becomes more prevalent with advancing age (approximately 7% in adults aged 60 years to 64 years; 8% for 65- to 69-year olds; 10% for 70- to 74-year olds; 15% for 75- to 79-year olds; and 25% for those 80 and older). Additionally, for adults older than 65 years with MCI, approximately 15% will develop dementia after 2 years. Among the few studies that report the natural history of MCI, between 15% and 38% of patients with MCI regress to normal. The panel identified 3 studies that assessed donepezil (Aricept), but could not pool data because of variable duration and variable outcome measures. These studies found little likelihood that donepezil prevents progression from MCI to Alzheimer dementia. Two studies assessed galantamine (Razadyne), and similarly failed to provide evidence that it slows progression to dementia. Only one trial evaluated rivastigmine (Exelon). After 4 years the rate of progression from MCI to dementia was similar for placebo-treated patients. A single trial evaluated a flavonoid-containing beverage, but that study duration was only 8 weeks, so we can't really conclude much. Additional studies with limited data included homocysteine-lowering vitamin B, nicotine patches, piribedil (an anti-Parkinson agent sold under many trade names), rofecoxib (Vioxx), growth hormone–releasing hormones, and various other vitamins. Most studies either showed the treatments were ineffective or were too short or too limited to have much faith in their results. The panel identified 7 studies of nonpharmacologic interventions. Only exercise seemed to show any short-term improvements. Cognitive interventions were too variable in scope, quality, and generalizability to recommend widespread adoption. Although this guideline was funded by the AAN, most of the panelists had financial ties to industry.
Bottom line: MCI follows a variable course: not all patients progress to dementia. The data on pharmacologic interventions are limited and, so far, not very encouraging. Of the nonpharmacologic interventions, the best, albeit limited, data support exercise.
Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018;90(3):126-135.

9. Blood pressure control and lipid lowering does not prevent cognitive decline (HOPE-3)

Clinical question: Does long-term blood pressure lowering and lipid lowering prevent cognitive decline in the elderly?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (any)
Synopsis: This report presents the long-term follow-up results from a subgroup of the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial. HOPE-3 included men at least 55 years of age and women at least 65 years of age with at least one additional clinical cardiovascular risk factor (or women at least 60 years of age with 2 additional risk factors). This report focuses on cognitive function in patients who were at least 70 years of age at the time of enrollment. Following a 4-week active treatment run-in period (you know by now that active run-ins can stack the deck in favor of the intervention), the researchers randomized patients to receive candesartan/hydrochlorothiazide 16/12.5 mg daily plus placebo (n = 593), rosuvastatin 10 mg daily plus placebo (n = 594), both active drugs (n = 587), or double placebo (n = 587). After the initial 6-week follow-up, the researchers assessed the patients every 6 months until the completion of HOPE-3 using 3 different standardized tools of cognitive function. Additionally, the researchers assessed the patients' functional status at baseline and at the end of the trial. At the end of the study, they had complete follow-up on only 69% of the enrolled patients, 9% of whom died. Among the remaining patients, after a median of 5.7 years of follow-up, the degree of change from baseline in any of the cognitive or functional measures was comparable in each of the 4 treatment groups. Candesartan/HCTZ lowered blood pressure by 6 mm Hg more than placebo, and rosuvastatin lowered low-density lipoprotein cholesterol by 25 mg/dL more than placebo. Although some early case-control studies have suggested an association between statins and the development of dementia, neither cohort studies nor clinical trials, including this one, have found such an association.
Bottom line: In this randomized trial, after a median of 5.7 years of follow-up, lowering blood pressure with candesartan/HCTZ and lowering cholesterol with rosuvastatin had no meaningful effect on cognition or function in the elderly.

Bosch J, O'Donnell M, Swaminathan B, et al, for the HOPE-3 Investigators. Effects of blood pressure and lipid lowering on cognition: Results from the HOPE-3 study. Neurology 2019;92(13):e1435-e1446.

10. Vitamin D = placebo for preventing cognitive decline in African-American women with low levels

Clinical question: Is vitamin D more effective than placebo in preventing cognitive decline in African-American women older than 65 years who have low serum vitamin D levels at baseline?
Bottom line: No.
Study design: Randomized controlled trial (double-blinded) **Funding source:** Government
Synopsis: These authors recruited African-American women from various community settings. During a pre-enrollment telephone interview, women were asked not to take vitamin D–containing supplements for 4 to 6 weeks before the study. The researchers then measured their serum vitamin D levels and included those women with levels between 8 ng/mL and 26 ng/mL. They excluded women with hip osteoporosis, Mini-Mental State Examination (MMSE) scores of less than 21, moderate to severe vertebral fractures, liver disease, or kidney stones. The researchers randomly assigned half the women to receive daily vitamin D3 (2400 IU, 3600 IU, or 4800 IU); n = 130) and the other half to receive matching placebo (n = 130). They used the baseline vitamin D level to determine the initial dose, then titrated the dose every 3 months to achieve a target level of 30 ng/mL. They also gave women in each group 1200 mg calcium daily. The researchers assessed the MMSE score every 6 months for 3 years and used a score of less than 27 as the cutoff for mild cognitive impairment. Unfortunately, 74 women dropped out of the study, which raises serious concerns about trusting the final results. Among the women who completed the study, the MMSE scores increased in both groups and the degree of improvement was comparable. The authors report no vitamin D–related adverse events. The authors, unfortunately, don't provide sample size or power estimates for the study. Finally, they properly recognize the limitations of the MMSE in detecting cognitive decline.
Owusu JE, Islam S, Katumuluwa SS, et al. Cognition and vitamin D in older African-American women—physical performance and osteoporosis prevention with vitamin D in older African Americans trial and dementia. J Am Geriatr Soc 2019;67(1):81-86.

11. Poor-quality data suggest that anticholinergic medications are associated with dementia and cognitive decline in the elderly

Clinical question: Are medications with anticholinergic properties associated with the development of dementia, mild cognitive impairment, or cognitive decline?
Study design: Meta-analysis (other) **Funding source:** Foundation
Synopsis: To update their previous systematic review, these authors searched 2 databases to identify studies published since 2013 that evaluated the effects of anticholinergic medications adults. The studies needed to be longer than 12 weeks' duration and address dementia, mild cognitive impairment, or cognitive decline. Two authors independently evaluated the studies for possible inclusion. The authors used the Cochrane Risk of Bias tool to assess the methodologic quality of the included studies. In addition to the 46 studies from their previous review, the authors identified 26 "new" studies (621,548 participants; mean study duration of 73 months). Overall, the studies were of pathetic quality. Only one was at moderate risk of bias; the remainder were at serious or critical risk of bias. The good news is that the studies actually assessed the outcomes well. Eleven studies that evaluated dementia presented poolable data. Although they found substantial heterogeneity, the authors report that, depending on the duration of use, anticholinergic drugs were associated with a higher likelihood of developing dementia (relative risks ranged from 1.20 to 1.50 with narrow confidence intervals). They identified 6 studies that evaluated the development of mild cognitive impairment and found no association with anticholinergic drugs. Twelve of the studies evaluated cognitive decline, mainly based on changes on the Mini-Mental Status Examination. The authors report greater cognitive decline was consistently found among users of anticholinergic drugs. Final comment: In their previous systematic review, the authors identified 46 smaller studies, but the quality ranged from poor to very good. Newer isn't always better.
Bottom line: The poor-quality studies identified in this meta-analysis indicate that anticholinergic drugs are associated with a greater likelihood of developing dementia and worsening cognitive function.
Pieper NT, Grossi CM, Chan WY, et al. Anticholinergic drugs and incident dementia, mild cognitive impairment and cognitive decline: a meta-analysis. Age Ageing 2020;49(6):939-947.

12. Multi-domain interventions for the prevention of dementia and cognitive decline

Background: Dementia is a worldwide concern. Its global prevalence is increasing. Currently, no effective medical treatment exists to cure or to delay the onset of cognitive decline or dementia. Up to 40% of dementia is attributable to potentially modifiable risk factors, which has led to the notion that targeting these risk factors might reduce the incidence of cognitive decline and dementia. Since sporadic dementia is a multifactorial condition, thought to derive from multiple causes and risk factors, multi-domain interventions may be more effective for the prevention of dementia than those targeting single risk factors. **Objectives:** To assess the effects of multi-domain interventions for the prevention of cognitive decline and dementia in older adults, including both unselected populations and populations at increased risk of cognitive decline and dementia.
Search methods: We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register, MEDLINE (Ovid SP), Embase (Ovid SP), PsycINFO (Ovid SP), CINAHL (EBSCOhost), Web of Science Core Collection (ISI Web of Science), LILACS (BIREME), and ClinicalTrials.gov on 28 April 2021. We also reviewed citations of reference lists of included studies, landmark papers, and review papers to identify additional studies and assessed their suitability for inclusion in the review. **Selection criteria:** We defined a multi-domain intervention as an intervention with more than one component, pharmacological or non-pharmacological, but not consisting only of two or more drugs with the same therapeutic target. We included randomised controlled trials (RCTs) evaluating the effect of such an intervention on cognitive functioning and/or incident dementia. We accepted as control conditions any sham intervention or usual care, but not single-domain interventions intended to reduce dementia risk. We required studies to have a minimum of 400 participants and an intervention and follow-up duration of at least 12 months. **Data collection and analysis:** We initially screened search results using a ‘crowdsourcing’ method in which members of Cochrane’s citizen science platform identify RCTs. We screened the identified citations against inclusion criteria by two review authors working independently. At least two review

authors also independently extracted data, assessed the risk of bias and applied the GRADE approach to assess the certainty of evidence. We defined high-certainty reviews as trials with a low risk of bias across all domains other than blinding of participants and personnel involved in administering the intervention (because lifestyle interventions are difficult to blind). Critical outcomes were incident dementia, incident mild cognitive impairment (MCI), cognitive decline measured with any validated measure, and mortality. Important outcomes included adverse events (e.g. cardiovascular events), quality of life, and activities of daily living (ADL). Where appropriate, we synthesised data in random-effects meta-analyses. We expressed treatment effects as risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs).
Main results: We included nine RCTs (18,452 participants) in this review. Two studies reported incident dementia as an outcome; all nine studies reported a measure for cognitive functioning. Assessment of cognitive functioning was very heterogeneous across studies, ranging from complete neuropsychological assessments to short screening tests such as the mini-mental state examination (MMSE). The duration of the interventions varied from 12 months to 10 years.
We compared multi-domain interventions against usual care or a sham intervention. Positive MDs and RRs <1 favour multi-domain interventions over control interventions. For incident dementia, there was no evidence of a difference between the multi-domain intervention group and the control group (RR 0.94, 95% CI 0.76 to 1.18; 2 studies; 7256 participants; high-certainty evidence). There was a small difference in composite Z-score for cognitive function measured with a neuropsychological test battery (NTB) (MD 0.03, 95% CI 0.01 to 0.06; 3 studies; 4617 participants; high-certainty evidence) and with the Montreal Cognitive Assessment (MoCA) scale (MD 0.76 point, 95% CI 0.05 to 1.46; 2 studies; 1554 participants), but the certainty of evidence for the MoCA was very low (due to serious risk of bias, inconsistency and indirectness) and there was no evidence of an effect on the MMSE (MD 0.02 point, 95% CI -0.06 to 0.09; 6 studies; 8697participants; moderate-certainty evidence). There was no evidence of an effect on mortality (RR 0.93, 95% CI 0.84 to 1.04; 4 studies; 11,487 participants; high-certainty evidence).
There was high-certainty evidence for an interaction of the multi-domain intervention with ApoE4 status on the outcome of cognitive function measured with an NTB (carriers MD 0.14, 95% CI 0.04 to 0.25, noncarriers MD 0.04, 95% CI -0.02 to 0.10, P for interaction 0.09). There was no clear evidence for an interaction with baseline cognitive status (defined by MMSE-score) on cognitive function measured with an NTB (low baseline MMSE group MD 0.06, 95% CI 0.01 to 0.11, high baseline MMSE group MD 0.01, 95% CI -0.01 to 0.04, P for interaction 0.12), nor was there clear evidence for an effect in participants with a Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score > 6 points (MD 0.07, 95%CI -0.00 to 0.15).
Authors' conclusions: We found no evidence that multi-domain interventions can prevent incident dementia based on two trials. There was a small improvement in cognitive function assessed by a NTB in the group of participants receiving a multi-domain intervention, although this effect was strongest in trials offering cognitive training within the multi-domain intervention, making it difficult to rule out a potential learning effect. Interventions were diverse in terms of their components and intensity.
Hafdi M, Hoevenaar-Blom MP, Richard E. Multi-domain interventions for the prevention of dementia and cognitive decline. Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD013572. DOI: 10.1002/14651858.CD013572.pub2.

Dementia

13. USPSTF 2020 does not recommend for or against screening for cognitive impairment in older adults (I Recommendation)

Clinical question: Should primary care clinicians screen for cognitive impairment in community-dwelling adults 65 years or older?
Study design: Practice guideline
Synopsis: In this updated review, the task force found one randomized clinical trial (n = 4005) that directly assessed the effect of screening for cognitive impairment on patient-oriented outcomes. No significant differences occurred in health-related quality of life at 6 months or 12 months, health care use, or measures of advance-care planning in the screening groups versus the control groups. Adequate evidence is available that some screening tools have high sensitivity and specificity for the detection of dementia. However, the task force evaluated the effects of various pharmacologic and nonpharmacologic treatment regimens and found only minimal changes that were not considered clinically important. In addition, interventions to support caregivers also have a small effect — the clinical importance of which remains uncertain. No direct evidence of harm from screening was found. The American Academy of Family Physicians supports the 2014 USPSTF recommendation, which is similar to this update. The American Academy of Neurology currently recommends assessing for cognitive impairment.
Bottom line: In this updated 2020 review, the US Preventive Services Task Force (USPSTF) found insufficient evidence to assess the balance of benefits and harms of screening for cognitive impairment in community-dwelling adults 65 years or older, including those residing in independent living facilities (I recommendation). This recommendation only applies to older adults without recognized signs or symptoms of cognitive impairment. These recommendations are consistent with the 2014 USPSTF recommendation statement.
US Preventive Services Task Force. Screening for cognitive impairment in older adults. US Preventive Services Task Force recommendation statement. JAMA 2020;323(8):757-763.

14. Aspirin does not reduce composite of death, disability, and dementia in older patients; increases bleeding risk (ASPREE)

Clinical question: Does aspirin improve disability-free survival in an otherwise healthy older person?
Study design: Randomized controlled trial (double-blinded)
Synopsis: These are the initial results of the landmark Aspirin in Reducing Events in the Elderly (ASPREE) trial. Two other reports describe the effect of aspirin on all-cause mortality and on cardiovascular disease. The authors randomized 19,114 community-dwelling adults to receive either 100 mg of enteric-coated aspirin or placebo. The study was conducted in the United States and Australia, with patients recruited between 2010 and 2014. Participants were 70 years or older (65 years or older if black or Hispanic in the United States, because of their shorter average lifespan), had no serious comorbidity that would be expected to limit their life expectancy to less than 5 years, and no known cardiovascular (CV) or cerebrovascular disease, dementia, high bleeding risk, or contraindication to

aspirin. The study included a 1-month placebo run-in period to ensure at least 80% adherence to the study medication. During the run-in period, 4049 patients were excluded, 61% because they failed adherence. Included patients were contacted every 3 months to further encourage adherence and to gather interim data. Outcomes were adjudicated by a committee masked to treatment assignment. The median age of participants was 74 years, 56% were women, and 8.7% were non-white. Most of the patients were recruited in Australia (87%), 74% had hypertension, 65% had hyperlipidemia, and only 11% had diabetes. Participants were followed up for a median of 4.8 years, and only 2.2% withdrew or were lost to follow-up. The primary outcome was a composite of death, dementia, or physical disability, which occurred in 921 persons who received aspirin and 914 who received placebo (hazard ratio [HR] 1.10; 95% CI 0.92 - 1.11). All-cause mortality was slightly higher in the aspirin group (12.7 vs 11.1 events per 1000 person-years; HR 1.14, 1.01 - 1.29; number needed to treat to harm [NNTH] = 625 per year). Major hemorrhage was more common in the aspirin group (8.6 vs 6.2 events per 1000 person-years; hazard ratio 1.38; 95% CI 1.18 - 1.62; number needed to treat to harm = 417 per year).
Bottom line: This landmark study found that in a contemporary population where risk factors such as hyperlipidemia and hypertension are more likely to be addressed, aspirin did not provide a benefit in terms of mortality, dementia, or disability in a largely white group of older patients.
McNeil JJ, Woods RL, Nelson MR, et al, for the ASPREE Investigator Group. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018;379(16):1499-1508.

15. Some drugs slightly improve cognition in people with dementia; effects on behavioral or psychological symptoms remain unclear

Clinical question: Can drug treatments improve outcomes in people with dementia?
Study design: Meta-analysis (randomized controlled trials)
Synopsis: These authors searched 4 databases, including the Cochrane Library, along with a clinical trials database and bibliographies of other systematic reviews, to identify all English-language studies of drug treatment to treat cognition, function, or behavioral and psychological symptoms associated with Alzheimer's-type dementia. Two authors screened possible articles for inclusion. One author performed data extraction, which was verified by a second author. The authors assessed risk of bias and only analyzed results from studies with low or medium risk, removing 97 of the 163 unique studies they identified. Regarding cognition, the researchers found a small improvement (standardized mean difference 0.30) with a low strength of evidence, though no effect on overall function or global clinical impression, with cholinesterase inhibitors. The most frequently studied cholinesterase inhibitor was donepezil (Aricept). In patients with moderate to severe disease, adding memantine to a cholinesterase inhibitor improved cognition and overall clinical impression, but not function as compared with placebo. No treatments had sufficient evidence of their benefit on behavioral or psychological symptoms. Withdrawal from treatment because of side effects was higher with cholinesterase inhibitors, primarily galantamine (Razadyne, Reminyl) and rivastigmine (Exelon), as compared with placebo. There was not significant heterogeneity among the studies. The likelihood of publication bias was not reported.
Bottom line: Some treatments can improve cognition on research scales, but daily function will not be affected in a noticeable way. Managing behavioral or psychological issues with medication is not supported by current evidence.
Fink HA, Linskens EJ, MacDonald R, et al. Benefits and harms of prescription drugs and supplements for treatment of clinical Alzheimer-type dementia. A systematic review and meta-analysis. Ann Intern Med 2020;172(10):656-668.

16. Withdrawing or continuing cholinesterase inhibitors, memantine or both, in people with dementia

Background: Dementia is a progressive syndrome characterised by deterioration in memory, thinking and behaviour, and by impaired ability to perform daily activities. Two classes of drug - cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and memantine - are widely licensed for dementia due to Alzheimer's disease, and rivastigmine is also licensed for Parkinson's disease dementia. These drugs are prescribed to alleviate symptoms and delay disease progression in these and sometimes in other forms of dementia. There are uncertainties about the benefits and adverse effects of these drugs in the long term and in severe dementia, about effects of withdrawal, and about the most appropriate time to discontinue treatment. **Objectives:** To evaluate the effects of withdrawal or continuation of cholinesterase inhibitors or memantine, or both, in people with dementia on cognitive, neuropsychiatric and functional outcomes, rates of institutionalisation, adverse events, dropout from trials, mortality, quality of life and carer-related outcomes.
Search methods: We searched the Cochrane Dementia and Cognitive Improvement Group's Specialised Register up to 17 October 2020 using terms appropriate for the retrieval of studies of cholinesterase inhibitors or memantine. The Specialised Register contains records of clinical trials identified from monthly searches of a number of major healthcare databases, numerous trial registries and grey literature sources. **Selection criteria:** We included all randomised, controlled clinical trials (RCTs) which compared withdrawal of cholinesterase inhibitors or memantine, or both, with continuation of the same drug or drugs. **Data collection and analysis:** Two review authors independently assessed citations and full-text articles for inclusion, extracted data from included trials and assessed risk of bias using the Cochrane risk of bias tool. Where trials were sufficiently similar, we pooled data for outcomes in the short term (up to 2 months after randomisation), medium term (3-11 months) and long term (12 months or more). We assessed the overall certainty of the evidence for each outcome using GRADE methods.
Main results: We included six trials investigating cholinesterase inhibitor withdrawal, and one trial investigating withdrawal of either donepezil or memantine. No trials assessed withdrawal of memantine only. Drugs were withdrawn abruptly in five trials and stepwise in two trials. All participants had dementia due to Alzheimer's disease, with severities ranging from mild to very severe, and were taking cholinesterase inhibitors without known adverse effects at baseline. The included trials randomised 759 participants to treatment groups relevant to this review. Study duration ranged from 6 weeks to 12 months. There were too few studies to allow planned subgroup analyses. We considered some studies to be at unclear or high risk of selection, performance, detection, attrition or reporting bias. Compared to continuing cholinesterase inhibitors, discontinuing treatment may be associated with worse cognitive function in the short term (standardised mean difference (SMD) -0.42, 95% confidence interval (CI) -0.64 to -0.21; 4 studies; low certainty), but the effect in the medium term is very uncertain (SMD -0.40, 95% CI -0.87 to 0.07; 3 studies; very low certainty). In a sensitivity analysis omitting data from a study which only included participants who had shown a relatively poor prior response to donepezil, inconsistency was reduced, and we found that cognitive function may be worse in the discontinuation group in the medium term (SMD -0.62; 95% CI -0.94

to -0.31). Data from one longer-term study suggest that discontinuing a cholinesterase inhibitor is probably associated with worse cognitive function at 12 months (mean difference (MD) -2.09 Standardised Mini-Mental State Examination (SMMSE) points, 95% CI -3.43 to -0.75; moderate certainty).
Discontinuation may make little or no difference to functional status in the short term (SMD -0.25, 95% CI -0.54 to 0.04; 2 studies; low certainty), and its effect in the medium term is uncertain (SMD -0.38, 95% CI -0.74 to -0.01; 2 studies; very low certainty). After 12 months, discontinuing a cholinesterase inhibitor probably results in greater functional impairment than continuing treatment (MD -3.38 Bristol Activities of Daily Living Scale (BADLS) points, 95% CI -6.67 to -0.10; one study; moderate certainty). Discontinuation may be associated with a worsening of neuropsychiatric symptoms over the short term and medium term, although we cannot exclude a minimal effect (SMD - 0.48, 95% CI -0.82 to -0.13; 2 studies; low certainty; and SMD -0.27, 95% CI -0.47 to -0.08; 3 studies; low certainty, respectively). Data from one study suggest that discontinuing a cholinesterase inhibitor may result in little to no change in neuropsychiatric status at 12 months (MD -0.87 Neuropsychiatric Inventory (NPI) points; 95% CI -8.42 to 6.68; moderate certainty).
We found no clear evidence of an effect of discontinuation on dropout due to lack of medication efficacy or deterioration in overall medical condition (odds ratio (OR) 1.53, 95% CI 0.84 to 2.76; 4 studies; low certainty), on number of adverse events (OR 0.85, 95% CI 0.57 to 1.27; 4 studies; low certainty) or serious adverse events (OR 0.80, 95% CI 0.46 to 1.39; 4 studies; low certainty), and on mortality (OR 0.75, 95% CI 0.36 to 1.55; 5 studies; low certainty). Institutionalisation was reported in one trial, but it was not possible to extract data for the groups relevant to this review.
Authors' conclusions: This review suggests that discontinuing cholinesterase inhibitors may result in worse cognitive, neuropsychiatric and functional status than continuing treatment, although this is supported by limited evidence, almost all of low or very low certainty. As all participants had dementia due to Alzheimer's disease, our findings are not transferable to other dementia types. We were unable to determine whether the effects of discontinuing cholinesterase inhibitors differed with baseline dementia severity. There is currently no evidence to guide decisions about discontinuing memantine. There is a need for further well-designed RCTs, across a range of dementia severities and settings. We are aware of two ongoing registered trials. In making decisions about discontinuing these drugs, clinicians should exercise caution, considering the evidence from existing trials along with other factors important to patients and their carers.
Parsons C, Lim WY, Loy C, McGuinness B, Passmore P, Ward SA, Hughes C. Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD009081. DOI: 10.1002/14651858.CD009081.pub2.

17. Nonpharmacologic approaches are better than medication to control aggression/agitation

Clinical question: What is the best approach to agitated patients with dementia?
Study design: Systematic review
Synopsis: The authors searched 5 databases, including Cochrane CENTRAL and bibliographies of retrieved studies, identifying 163 randomized controlled studies of 23,143 patients that compared interventions for treating aggression and agitation in adults with dementia. Two investigators independently selected, abstracted, and evaluated the studies. Almost half of the studies were categorized as being at high risk of bias, mostly because of missing outcome data. Since not every intervention is directly compared with one another, the authors performed a network analysis, which allows indirect comparisons based on a common comparator. Typical antipsychotics provided no additional benefit compared with modifying instrumental activities of daily living (which is also not more effective than usual care). Cannabinoids and dextromethorphan/quinidine were moderately more effective than instrumental activity of daily living modification. Outdoor activity, multidisciplinary care, and massage and touch therapy, with or without music, were effective in producing a large reduction in aggression and agitation.
Bottom line: Hold the Haldol. Nonpharmacologic approaches to agitated or aggressive patients with dementia are more effective than medication. Outdoor activities, multidisciplinary care, and massage and touch therapy with or without music are all effective.
Watt JA, Goodarzi Z, Veroniki AA, et al. Comparative efficacy of interventions for aggressive and agitated behaviors in dementia. A systematic review and network meta-analysis. Ann Intern Med 2019;171(9):633-642.

18. Mirtazapine does not reduce agitated behaviors in persons with dementia (SYMBAD)

Clinical Question: Does mirtazapine reduce agitated behaviors in persons with dementia?
Study Design: Randomized controlled trial (double-blinded) **Funding:** Government
Synopsis: This was a well-designed randomized controlled trial of mirtazapine versus placebo for the treatment of agitation among 204 people with dementia. It was conducted in 26 UK National Health Service clinical centers over 12 weeks. Participants were enrolled if they met the criteria from the National Institute of Neurological and Communicative Diseases and Stroke – Alzheimer's Disease and Related Disorders Association for probable or possible Alzheimer's disease and had coexisting agitation defined as a Cohen-Mansfield Agitation Inventory (CMAI) score of at least 45. The investigators also required that the agitated behaviors had not responded to nonpharmacological management. Potential participants were excluded if they were considered too unwell (e.g., suicide risk), had medical contraindications, or did not have a family or professional caregiver to provide information. The target dose was 45 mg daily of mirtazapine, three 15-mg capsules in one daily dose or identical-appearing placebo. The authors started with one capsule daily and increased by one capsule daily in weeks 2 and 3, as tolerated. They allowed additional titration as needed. Analysis was by intention to treat. Adequate clinical response was defined as improvement by at least 6 points on the CMAI at the 12-week follow-up. The mean dose in the treated group was 30.5 mg. The severity of agitation improved in both groups over time and at no point reached a statistically significant difference. Caregiver burden was not lower in the treated group at any point, including no difference in anxiety. There were several more deaths in the treated group (7 vs 1), but the study was not powered to assess this outcome.
Bottom Line: Mirtazapine did not reduce agitated behaviors among persons with dementia nor reduce caregiver burden. There were more deaths in the treated group, which (even though the number was not statistically significant) warrants caution with the use of this medication in persons with dementia.
Banerjee S, High J, Stirling S, et al. Study of mirtazapine for agitated behavior in dementia (SYMBAD): a randomized, double-blind, placebo-controlled trial. Lancet 2021;398(10310):1487-1497.

19. Aducanumab

In 2021, the FDA approved a new drug, aducanumab (Aduhelm®), for the treatment of persons with dementia, eventually modifying the indication to those with mild dementia. This was not without controversy. As of February 26, 2022, there have been ***zero*** published randomized trials that used any clinically relevant endpoint. However, ClinicalTrials.gov reports 11 studies: 4 are completed and assess dose finding and bioavailability; 4 were terminated; 2 are recruiting participants; 1 is finished with recruitment and still active. At the time of this writing, the only outcomes reported in peer-reviewed literature was amyloid deposition. Ebell and Barry (*Am Fam Physician.* 2022;105(4):353-354.) used data provided to the FDA and found data on changes in the Mini Mental Status Exam and other clinically relevant measures of cognition: no clinically meaningful improvements were reported. However, the drug caused amyloid-related imaging abnormalities including edema (35% of treated patients) and hemorrhage (21% of treated patients). These changes were associated in some patients with headache (47%), confusion (15%), dizziness (11%) and nausea (8%). It is administered via monthly infusion (10 mg/kg) and thee estimated average cost initially was $56,000 per year. In December 2021, the manufacturer announced a price reduction to $28,200/year.

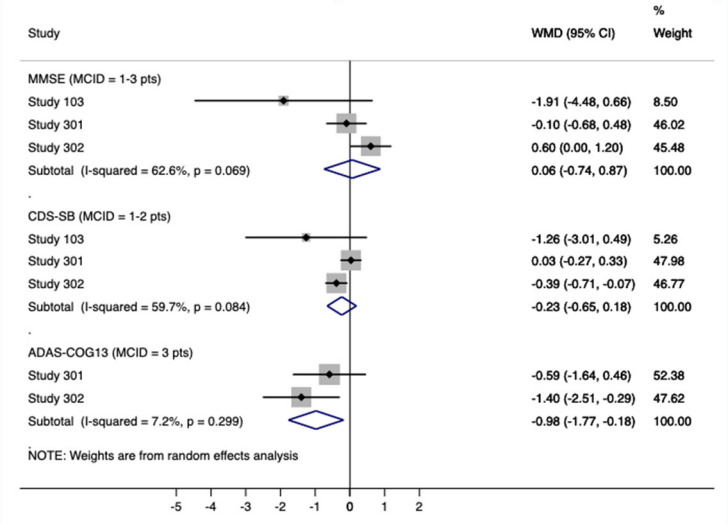


Figure 1. Forest plot of weighted mean differences (WMD) in points for aducanumab versus placebo for 3 dementia rating scales. An increase in the MMSE indicates improvement in the aducanumab group, while a decrease in the CDS-SB and ADAS-COG13 scales indicates improvement in the aducanumab group.
Note: MMSE = Mini-Mental State Examination, CDS-SB = Clinical Dementia Score Sum of Boxes, and ADAS-COG13 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-13 items. MCID = minimal clinically important difference from the published literature.

Bottom Lines:

- Consider referring a patient to palliative care if you would not be surprised the person would die within a year.
- Facilitating advanced care planning and execution of advanced directives is feasible in practice and through online modules for those with access
- Up to 1/3 of persons with mild cognitive impairment will actually develop normal cognition
- Interventions to prevent dementia are disappointing (BP lowering, statins, aspirin, medications, multi-domain interventions, etc.)
- While the effectiveness of adding cholinesterase inhibitors or memantine does not seem to do much for persons with dementia, limited data suggests that withdrawing them worsens cognition and function
- So far, the newly FDA-approved drug aducanumab has no meaningful effect on measures of cognition.

Upper GI Update — Gary Ferenchick MD

Learning objectives: Understand:

- Highlights from consensus documents on *H pylori*
- *H pylori* is the major risk factor for gastric cancer (GC)
- Eradication of HP is associated with less risk for GC

In the past several years, major consensus reports and guidelines on H pylori infection have been published. Highlights from each of these three documents are outlined below

Bottom line: All H pylori infections should be considered pathogenic and should be eradicated

Summary Highlights from Kyoto global consensus report (2015) | Maastricht V/Florence Consensus Report (2017) | American College of Gastroenterology (2017) | Taipei Global Consensus (2020) (See appendix)

- *H. pylori infection* is a common bacterial infection of the human stomach that affects more than half the world population (e.g., ~ 80% Africa, 55% Asia, 37% N America).
- Most *H. pylori* infections are acquired before the age of 10 producing a chronic infection that may remain clinically unapparent or evolve into severe complications.
- The rate of progression is unpredictable and most patients with chronic gastritis may remain asymptomatic until the appearance of severe complications.
- *H. pylori* is a class 1 human carcinogen, responsible for ~ 90% of human gastric cancers worldwide
- Gastric cancer is the 5th most common cancer and 3rd leading cause of cancer deaths worldwide
- Importantly, it is now established that eradication of *H. pylori* reduces the risk of gastric cancer development

#1 The overall prevalence of H Pylori worldwide is 44%

BACKGROUND: The epidemiology of Helicobacter pylori infection is poorly understood.
AIM: To establish the reported regional and national prevalence of H. pylori infection, stratified by age and gender.
METHODS: All relevant English publications from 2000 to 2017 cited by PubMed and Scopus were retrieved using comprehensive combinations of keywords. The overall prevalence of H. pylori was estimated using both random effect and fixed effect meta-analyses, and presented as prevalence rate (% and 95% CI). The analyses were extended by separation into gender and age groups.
RESULTS: A total of 14 056 records were obtained initially. After applying exclusion criteria in several steps, 183 studies were selected. Analysis of 410 879 participants from 73 countries in six continents revealed an overall prevalence of 44.3% (95% CI: 40.9-47.7) worldwide. This rate ranged from 50.8% (95% CI: 46.8-54.7) in developing countries compared with 34.7% (95% CI: 30.2-39.3) in developed countries. The global H. pylori infection rate was 42.7% (95% CI: 39-46.5) in females compared to 46.3% (95% CI: 42.1-50.5) in males. The prevalence in adults (≥18 years) was significantly higher than in children (48.6% [95% CI: 43.8-53.5] vs 32.6% [95% CI: 28.4-36.8], respectively). There was a statistically nonsignificant decrease in the prevalence in 2009-2016 compared to 2000-2009.
CONCLUSIONS: The observed differences between countries appear to be due to economic and social conditions. H. pylori infection can be a benchmark for the socioeconomic and health status of a country. Further studies are suggested to investigate the natural history of the acquisition of H. pylori infection from childhood into adult life.
REFERENCE: Zamani M et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther. 2018 Apr;47(7):868-876.

According to the AGA "it is often difficult to know what the H. pylori prevalence is in the local population"

H Pylori and Gastric Cancer

Gastric cancer is preventable through the eradication of *H pylori*. The following studies all demonstrate that GC risk reduction is greatest many years after H pylori treatment.

#2 Cohort Study: Treating H Pylori associated with lower gastric cancer risk

BACKGROUND: Helicobacter pylori (H. pylori) is considered to be the most important risk factor for gastric cancer (GC). The International Agency for Research on Cancer reported that H. pylori eradication could reduce the risk of developing GC. Several clinical studies have investigated this relationship as well; however, their results are inconsistent owing to the varied inclusion criteria. To address the effect of H. pylori eradication on GC incidence, we conducted a comprehensive meta-analysis with several subgroup analyses to resolve these inconsistencies.
METHODS: We searched MEDLINE and Ichushi-Web to identify randomized control trial and cohort study articles (English or Japanese) through December 2016. Manual searches were also conducted to identify unlisted references in these databases. Eligible studies reported GC incidence as an outcome, with comparisons between H.pylori eradication and control groups. Subgroup analyses were conducted by country, conditions at baseline, and follow-up periods.
RESULTS: We selected 28 studies among 1583 references in the databases and 4 studies by manual searches. The H. pylori eradication group showed significantly lower risk of GC [odds ratio (OR) 0.46; 95% confidence interval 0.39-0.55]. The subgroup analyses indicated that the beneficial effect of eradication was greater in Japan (OR 0.39; 95% CI 0.31-0.49), particularly among those with benign conditions (OR 0.32; 95% CI 0.19-0.54), although none of them was statistically significant. However, reduction of gastric cancer after eradication was significantly greater ($p = 0.01$) in the groups with long-term (5 years or longer) follow-up (OR 0.32; 95% CI 0.24-0.43) as compared to those with shorter follow-up (less than 5 years) (OR 0.55; 95% CI 0.41-0.72).
CONCLUSION: Real world data showed that large-scale eradication therapy has been performed mostly for benign conditions in Japan. Since eradication effects in preventing gastric cancer are conceivably greater there, GC incidence may decline faster in Japan than expected from the previous meta-analyses data which were based on multi-national, mixed populations with differing screening quality and disease progression.
***REFERENCE**: Sugano K. Effect of Helicobacter pylori eradication on the incidence of gastric cancer: a systematic review and meta-analysis. Gastric Cancer 2019 May;22(3):435-445.*

#3 Cohort Study: Treating H Pylori associated with lower gastric cancer risk

Background: In Japan, there are ongoing efforts to shift the gastric cancer prevention and control policy priorities from barium-based screening to Helicobacter pylori (H. pylori)-oriented primary prevention. A comprehensive summary of the evidence regarding the effects of H. pylori eradication on the risk of gastric cancer could inform policy decisions.
Methods: We conducted a systematic review and meta-analysis of published studies evaluating the effectiveness of H. pylori eradication for the prevention of gastric cancer in otherwise healthy individuals (primary prevention) and early gastric cancer patients (tertiary prevention).
Results: In total, 19 studies were included. Three moderate-quality observational cohort studies showed that H. pylori eradication may be associated with a decreased risk of gastric cancer in healthy asymptomatic Japanese people. There is moderate certainty regarding the effectiveness of H. pylori eradication in patients with gastrointestinal diseases, such as peptic ulcers. A meta-analysis of 10 observational studies with otherwise healthy individuals (mainly peptic ulcer patients) yielded an overall odds ratio of 0.34 (95% CI: 0.25-0.46). For tertiary prevention, the overall odds ratio for developing metachronous gastric cancer was 0.42 (95% CI: 0.35-0.51) in the eradication group in a meta-analysis of nine studies involving early gastric cancer patients who underwent endoscopic resection.
Conclusion: H. pylori eradication is effective in preventing gastric cancer in the Japanese population, regardless of symptoms. Well-designed, large cohort studies are warranted to determine the long-term efficacy and safety of H. pylori eradication in the context of reducing the gastric cancer burden through population-based screening and treatment.
Reference: Effects of Helicobacter pylori eradication on gastric cancer incidence in the Japanese population: a systematic evidence review. Jpn J Clin Oncol. 2021 Jul 1;51(7):1158-1170.

#4 Cohort Study: Treating H Pylori associated with lower gastric cancer risk

Background & aims: Helicobacter pylori eradication and endoscopic surveillance of gastric precancerous lesions are strategies to reduce gastric cancer (GC) risk. To our knowledge, this study is the longest prospective cohort of an H pylori eradication trial in a Hispanic population.
Methods: A total of 800 adults with precancerous lesions were randomized to anti-H pylori treatment or placebo. Gastric biopsy samples taken at baseline and 3, 6, 12, 16, and 20 years were assessed by our Correa histopathology score. A generalized linear mixed model with a participant-level random intercept was used to estimate the effect of H pylori status on the score over time. Logistic regression models were used to estimate progression by baseline diagnosis and to estimate GC risk by intestinal metaplasia (IM) subtype and anatomic location.
Results: Overall, 356 individuals completed 20 years of follow-up. Anti-H pylori therapy (intention-to-treat) reduced progression of the Correa score (odds ratio [OR], 0.59; 95% confidence interval [CI], 0.38-0.93). H pylori-negative status had a beneficial effect on the score over time (P = .036). Among individuals with IM (including indefinite for dysplasia) at baseline, incidence rates per 100 person-years were 1.09 (95% CI, 0.85-1.33) for low-grade/high-grade dysplasia and 0.14 (95% CI, 0.06-0.22) for GC. Incomplete-type (vs complete-type) IM at baseline presented higher GC risk (OR, 13.4; 95% CI, 1.8-103.8). Individuals with corpus (vs antrum-restricted) IM showed an OR of 2.1 (95% CI, 0.7-6.6) for GC.
Conclusions: In a high-GC-risk Hispanic population, anti-H pylori therapy had a long-term beneficial effect against histologic progression. Incomplete IM is a strong predictor of GC risk.
Reference: Piazuelo MB et al. The Colombian Chemoprevention Trial: 20-Year Follow-Up of a Cohort of Patients With Gastric Precancerous Lesions. Gastroenterology. 2021 Mar;160(4):1106-1117.e3.

#5 Mass eradication of HP decreases gastric CA risk & mortality among populations

Objective: Although mass eradication of Helicobacter pylori has been proposed as a means to eliminate gastric cancer, its long-term effects remain unclear.
Design: Mass eradication of H. pylori infection was launched in 2004 and continued until 2018 for a high-risk Taiwanese population aged 30 years or older dwelling on Matsu Islands with prevalent H. pylori infection. Test positives for the 13C-urea breath test underwent eradication therapy. We evaluated the effectiveness of the mass eradication in reducing two main outcomes, incidence and mortality rates of gastric cancer, until the end of 2016 and 2018, respectively.
Results: After six rounds of mass screening and eradication, the coverage rate reached 85.5% (6512/7616). The referral rate for treatment was 93.5% (4286/4584). The prevalence rates of H. pylori fell from 64.2% to 15.0% with reinfection rates of less than 1% per person-year. The presence and severity of atrophic gastritis and intestinal metaplasia also decreased with time. Compared with the historical control period from 1995 to 2003, the effectiveness in reducing gastric cancer incidence and mortality during the chemoprevention period was 53% (95% CI 30% to 69%, p<0.001) and 25% (95% CI -14% to 51%, p=0.18), respectively. No significant changes were noted in the incidence rates of other digestive tract cancers or the antibiotic resistance rate of H. pylori.
Conclusion: Population-based eradication of H. pylori has significantly reduced gastric cancer incidence with no increase in the likelihood of adverse consequences. A significant reduction in mortality is likely to be achieved with a longer follow-up period.
Reference: Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. Gut. 2021 Feb;70(2):243-250.

#6 RCT: Treating H Pylori lowers gastric cancer recurrence risk

BACKGROUND: Patients with early gastric cancers that are limited to gastric mucosa or submucosa usually have an advanced loss of mucosal glandular tissue (glandular atrophy) and are at high risk for subsequent (metachronous) development of new gastric cancer. The long-term effects of treatment to eradicate Helicobacter pylori on histologic improvement and the prevention of metachronous gastric cancer remain unclear.
METHODS: In this prospective, double-blind, placebo-controlled, randomized trial, we assigned 470 patients who had undergone endoscopic resection of early gastric cancer or high-grade adenoma to receive either H. pylori eradication therapy with antibiotics or placebo. Two primary outcomes were the incidence of metachronous gastric cancer detected on endoscopy performed at the 1-year follow-up or later and improvement from baseline in the grade of glandular atrophy in the gastric corpus lesser curvature at the 3-year follow-up.
RESULTS: A total of 396 patients were included in the modified intention-to-treat analysis population (194 in the treatment group and 202 in placebo group). During a median follow-up of 5.9 years, metachronous gastric cancer developed in 14 patients (7.2%) in the treatment group and in 27 patients (13.4%) in the placebo group (hazard ratio in the treatment group, 0.50; 95% confidence interval, 0.26 to 0.94; P=0.03). Among the 327 patients in the subgroup that underwent histologic analysis, improvement from baseline in the atrophy grade at the gastric corpus lesser curvature was observed in 48.4% of the patients in the treatment group and in 15.0% of those in the placebo group (P<0.001). There were no serious adverse events; mild adverse events were more common in the treatment group (42.0% vs. 10.2%, P<0.001).
CONCLUSIONS: Patients with early gastric cancer who received H. pylori treatment had lower rates of metachronous gastric cancer and more improvement from baseline in the grade of gastric corpus atrophy than patients who received placebo.
(Funded by the National Cancer Center, South Korea; ClinicalTrials.gov number,NCT02407119 .).
REFERENCE: *Choi IJ et al. Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer. N Engl J Med. 2018 Mar 22;378(12):1085-1095. Comment in: N Engl J Med. 2018 Mar 22;378(12):1154-1156.*

#7 Treating family members of patients with H Pylori lowers gastric cancer risk

Background: *Helicobacter pylori* infection and a family history of gastric cancer are the main risk factors for gastric cancer. Whether treatment to eradicate *H. pylori* can reduce the risk of gastric cancer in persons with a family history of gastric cancer in first-degree relatives is unknown.
Methods: In this single-center, double-blind, placebo-controlled trial, we screened 3100 first-degree relatives of patients with gastric cancer. We randomly assigned 1838 participants with *H. pylori* infection to receive either eradication therapy (lansoprazole [30 mg], amoxicillin [1000 mg], and clarithromycin [500 mg], each taken twice daily for 7 days) or placebo. The primary outcome was development of gastric cancer. A prespecified secondary outcome was development of gastric cancer according to *H. pylori* eradication status, assessed during the follow-up period.
Results: A total of 1676 participants were included in the modified intention-to-treat population for the analysis of the primary outcome (832 in the treatment group and 844 in the placebo group). During a median follow-up of 9.2 years, gastric cancer developed in 10 participants (1.2%) in the treatment group and in 23 (2.7%) in the placebo group (hazard ratio, 0.45; 95% confidence interval [CI], 0.21 to 0.94; P = 0.03 by log-rank test). Among the 10 participants in the treatment group in whom gastric cancer developed, 5 (50.0%) had persistent *H. pylori* infection. Gastric cancer developed in 0.8% of participants (5 of 608) in whom *H. pylori* infection was eradicated and in 2.9% of participants (28 of 979) who had persistent infection (hazard ratio, 0.27; 95% CI, 0.10 to 0.70). Adverse events were mild and were more common in the treatment group than in the placebo group (53.0% vs. 19.1%; P<0.001).
Conclusions: Among persons with *H. pylori* infection who had a family history of gastric cancer in first-degree relatives, *H. pylori* eradication treatment reduced the risk of gastric cancer. (Funded by the National Cancer Center, South Korea; ClinicalTrials.gov number, NCT01678027.).
Reference: Family History of Gastric Cancer and Helicobacter pylori Treatment. Choi IJ et al. NEJM 2020 Jan 30;382(5):427-436.

From above
In this prospective, randomized trial involving first-degree relatives of patients with gastric cancer, the risk of gastric cancer was 55% lower among those who received H. pylori eradication treatment than among those who received placebo, during a median follow-up of 9.2 years. Of note, the risk of gastric cancer was 73% lower among persons in whom H. pylori eradication was achieved than among those in whom infection was persistent. Adverse events were common in the treatment group, but the severity was usually mild.

Other summary highlights

- Testing options
    - Urea breath test (UBT) is the most investigated and best recommended non-invasive test in the context of a 'test-and-treat strategy'.
    - Stool antigen tests (SATs) may less acceptable but has high sensitivity and specificity
        - PPIs should be discontinued for 2 weeks prior to testing (UBT AND SAT) as PPIs have anti-H. pylori activity leading to false negative tests.
    - No need to discontinue H2 blockers or antacids (aside from bismuth)
- Confirmation of eradication
    - UBT is the best option for confirmation of H. pylori eradication and monoclonal SAT is an alternative. It should be performed at least 4 weeks after completion of therapy. (Same PPI recommendations as above)

#8 Follow up for "test of cure" = rare

Background & aims: Expert consensus mandates retesting for eradication of Helicobacter pylori infection after treatment, but it is not clear how many patients are actually retested. We evaluated factors associated with retesting for H pylori in a large, nationwide cohort.
Methods: We performed a retrospective cohort study of patients with H pylori infection (detected by urea breath test, stool antigen, or pathology) who were prescribed an eradication regimen from January 1, 1994 through December 31, 2018 within the Veterans Health Administration (VHA). We collected data on demographic features, smoking history, socioeconomic status, facility poverty level and academic status, and provider specialties and professions. The primary outcome was retesting for eradication. Statistical analyses included mixed-effects logistic regression.
Results: Of 27,185 patients prescribed an H pylori eradication regimen, 6486 patients (23.9%) were retested. Among 7623 patients for whom we could identify the provider who ordered the test, 2663 patients (34.9%) received the order from a gastroenterological provider. Female sex (odds ratio, 1.22; 95% CI, 1.08-1.38; P = .002) and history of smoking (odds ratio, 1.24; 95% CI, 1.15-1.33; P < .001) were patient factors associated with retesting. There was an interaction between method of initial diagnosis of H pylori infection and provider who ordered the initial test (P < .001). There was significant variation in rates of retesting among VHA facilities (P < .001).
Conclusions: In an analysis of data from a VHA cohort of patients with H pylori infection, we found low rates of retesting after eradication treatment. There is significant variation in rates of retesting among VHA facilities. H pylori testing is ordered by nongastroenterology specialists two-thirds of the time. Confirming eradication of H pylori is mandatory and widespread quality assurance protocols are needed.
Reference: Low Rates of Retesting for Eradication of Helicobacter pylori Infection After Treatment in the Veterans Health Administration. Clin Gastroenterol Hepatol. 2021 Feb;19(2):305-313.e1

#9 Gastric Ca risk only decreased if eradication of HP was successful

Background & aims: Nearly all studies of gastric adenocarcinoma in the United States have relied on national cancer databases, which do not include data on Helicobacter pylori infection, the most well-known risk factor for gastric cancer. We collected data from a large cohort of patients in the United States to calculate the incidence of and risk factors for nonproximal gastric adenocarcinomas after detection of H pylori. Secondary aims included identifying how treatment and eradication affect cancer risk.
Methods: We performed a retrospective cohort study, collecting data from the Veterans Health Administration on 371,813 patients (median age 62 years; 92.3% male) who received a diagnosis of H pylori infection from January 1, 1994, through December 31, 2018. The primary outcome was a diagnosis of distal gastric adenocarcinoma 30 days or more after detection of H pylori infection. We performed a time to event with competing risk analysis (with death before cancer as a competing risk).
Results: The cumulative incidence of cancer at 5, 10, and 20 years after detection of H pylori infection was 0.37%, 0.5%, and 0.65%, respectively. Factors associated with cancer included older age at time of detection of H pylori infection (subhazard ratio [SHR], 1.13; 95% confidence interval [CI], 1.11-1.15; P < .001), black/African American race (SHR, 2.00; 95% CI, 1.80-2.22), Asian race (SHR, 2.52; 95% CI, 1.64-3.89) (P < .001 for race), Hispanic or Latino ethnicity (SHR, 1.59; 95% CI, 1.34-1.87; P < .001), and history of smoking (SHR, 1.38; 95% CI, 1.25-1.52; P < .001). Women had decreased risk of gastric adenocarcinoma compared with men (SHR, 0.52; 95% CI, 0.40-0.68; P < .001); patients whose H pylori infection was detected based on serum antibody positivity also had a reduced risk of cancer (SHR 0.74; 95% CI, 0.54-1.04; P = .04). Patients who received treatment for their H pylori infection still had an increased risk of gastric cancer (SHR, 1.16; 95% CI, 0.74-1.83; P = .51) but confirmed H pylori eradication after treatment reduced risk of gastric cancer (SHR, 0.24; 95% CI, 0.15-0.41; P < .001).
Conclusions: In a study of 371,813 veterans with a diagnosis of H pylori infection, we found significantly higher risks of gastric cancer in racial and ethnic minorities and smokers. Treatment of H pylori infection decreased risk only if eradication was successful. Studies are needed on the effects of screening high-risk persons and to identify quality measures for diagnosis, resistance patterns, and treatment efficacy.
Reference: Risk Factors and Incidence of Gastric Cancer After Detection of Helicobacter pylori Infection: A Large Cohort Study. Gastroenterology. 2020 Feb;158(3):527-536.e7.

Geographical distribution of antimicrobial resistance patterns per U.S. region, 2017-2018

Antibiotic	All isolates n=345	West n=108	Central n=86	East n=151	P-value
Amoxicillin	6.4% (22)	8.3% (9)	5.8% (5)	5.3% (8)	0.6
Clarithromycin	17.4% (60)	11.1% (12)	15.1% (13)	23.2% (35)	0.03
Metronidazole	43.6% (150)*	35.5% (38)*	43.0% (37)	49.7% (75)	0.08
Rifabutin	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	ND
	Limited Analysis n=71	n=19	n=19	n=33	
Tetracycline	2.8% (2)	5.3% (1)	5.3% (1)	0 (0.0%)	0.3
Levofloxacin	57.8% (41)	57.8% (11)	68.4% (13)	17 (51.5%)	0.5

National and Regional United States Antibiotic Resistance to Helicobacter pylori Resistance to Helicobacter pylori. Lessons from a Clinical Trial. Gastroenterology. 2021 Jul; 161(1): 342–344.e1.

#10 Antibiotic resistance to HP is a thing

Background: Although consensus supports eradication of *Helicobacter pylori* infections, antimicrobial resistance has substantially reduced eradication rates with most current therapies.
Objective: To assess the effectiveness of a novel rifabutin-based therapy (RHB-105) for *H pylori* eradication.
Design: Phase 3, double-blind trial (ERADICATE Hp2). (ClinicalTrials.gov: NCT03198507).
Setting: 55 clinical research sites in the United States.
Participants: 455 treatment-naive adults with epigastric discomfort and confirmed *H pylori* infection.
Intervention: RHB-105 (amoxicillin, 3 g; omeprazole, 120 mg; and rifabutin, 150 mg) versus active comparator (amoxicillin, 3 g, and omeprazole, 120 mg), given as 4 capsules every 8 hours for 14 days.
Measurements: Between-group difference for *H pylori* eradication rate, demonstrated by ^{13}C urea breath test 4 weeks after treatment, analyzed by using the χ^2 test.
Results: In the intention-to-treat population, the eradication rate was higher with RHB-105 than with the active comparator (228 vs. 227 patients, respectively; 83.8% [95% CI, 78.4% to 88.0%] vs. 57.7% [95% CI, 51.2% to 64.0%]; $P < 0.001$). Eradication rates were unaffected by resistance to clarithromycin or metronidazole. No rifabutin resistance was detected. The most commonly reported adverse events (incidence ≥5%) were diarrhea (10.1% with RHB-105 vs. 7.9% with active comparator), headache (7.5% vs. 7.0%), and nausea (4.8% vs. 5.3%).
Limitation: Persons of Asian descent were excluded because of their higher prevalence of poor cytochrome P450 2C19 metabolizers.
Conclusion: These findings suggest potential for RHB-105 as first-line empirical *H pylori* therapy, addressing an unmet need in the current environment of increasing antibiotic resistance.
Reference: Graham DY, Cannan Y, Maher J, et al. Rifabutin-based triple therapy (RHB-105) for Helicobacter pylori eradication: A double-blind, randomized, controlled trial. Ann Intern Med 2020;172:795–802.

In the case of H pylori, individualized treatment is limited by the fact that antibiotic sensitivity testing is not routinely available, forcing clinicians to use empirical therapies

- The prevalence of H pylori resistance to clarithromycin, metronidazole, and levofloxacin has increased to a level that, except in a few regions, these antibiotics are not considered appropriate for empirical use in triple therapies
- Given the high rates of resistance to clarithromycin, metronidazole, and levofloxacin, these should no longer be used in triple regimens unless based on susceptibility testing.
- In 2019, the FDA approved a 3-in-1 combination product of omeprazole, amoxicillin, and rifabutin for the treatment of *H. pylori* infection in adults

- Talicia® contains 12.5 milligrams (mg) of rifabutin, 250 mg of amoxicillin, and 10 mg of omeprazole. 4 capsules every 8 hours per day for 14 days with food,
    - Goodrx.com ~ $ 700 for 168 capsules

Other summary highlights

- Evidence exists linking *H. pylori* to unexplained iron deficiency anemia (IDA), idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency. In these disorders, H. pylori should be sought and eradicated"

#11 Another interesting connection to HP | Chronic urticaria

Objectives: The association between Helicobacter pylori and chronic spontaneous urticaria (CSU) is controversial. Therefore, we aimed to directly diagnose H pylori by polymerase chain reaction (PCR) in gastric tissue from patients with CSU and to investigate the association between H pylori eradication therapy and CSU remission.
Methods: Twenty-seven of 72 patients with CSU who were positive for H pylori stool antigen and PCR in gastric biopsy specimens were randomized to receive either anti-H pylori treatment or placebo.
Results: Patients with H pylori were found to have significantly lower hemoglobin concentrations with microcytic hypochromic anemia and a significantly higher occurrence of dyspepsia symptoms. All H pylori-treated patients (except two) showed significant improvement of the urticaria itching and red wheals after 2 weeks of therapy compared with the placebo group ($P < .001$). The response rate to treatment was 85.7% (12 patients; 95% confidence interval, 64.3%-100.0%). The two patients who failed to eradicate H pylori had an H pylori strain resistant to amoxicillin.
Conclusions: An association was observed between CSU and presence of H pylori infection in the gastric tissue. Whether this is a causal relationship or not remains to be discovered, but treatment of H pylori can significantly improve the symptoms of CSU.
Reference: Positive Effect of Helicobacter pylori Treatment on Outcome of Patients With Chronic Spontaneous Urticaria. Am J Clin Pathol. 2021 Feb 11;155(3):405-411.

GERD

The American College of Gastroenterology has published updated guidelines for GERD in 2022
Reference: ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease, Am J Gastroenterol 2022 Jan 1;117(1):27-56 (See appendix for points relevant for primary care)

12 Head of bed elevation = effective

Background: Overuse of proton pump inhibitors (PPIs) - frequently used for relieving symptoms of gastroesophageal reflux disease (GORD) - raises long-term safety concerns, warranting evidence-based non-drug interventions. We conducted a systematic review to evaluate the effect of head-of-bed elevation on relieving symptoms of GORD in adults.
Methods: We included controlled trials comparing the effect of head-of-bed elevation interventions to control in adults with GORD. Two independent reviewers screened articles, extracted data, and assessed quality of included studies. Primary outcomes were changes in GORD symptoms and use of PPIs.
Results: We screened 1206 records; and included five trials (four cross-over and one factorial) comprising 228 patients. All five included trials were judged to be at high-risk of performance bias and four of selection bias. Of five included trials, two used 'bed blocks' under the bed legs; one used 'sleeping on a wedge' pillow, and two used both. High heterogeneity in outcome measures and reported outcomes data precluded meta-analyses. The four studies that reported on GORD symptoms found an improvement among participants in the head-of-bed elevation; a high-quality crossover trial showed a clinical important reduction in symptom scores at 6 weeks (risk ratio of 2.1; 95% CI 1.2 to 3.6). These results are supported by the observed improvement in physiological intra-oesophageal pH measurements.
Conclusions: Methodological and reporting limitations in available literature preclude definitive recommendations. However, head-of-bed elevation could be still considered as a cheap and safe alternative to drug interventions with unfavourable safety profiles.
Reference: Head of bed elevation to relieve gastroesophageal reflux symptoms: a systematic review. BMC Fam Pract. 2021 Jan 19;22(1):24.

13 Diaphragmatic breathing and upright GERD = possibly effective

Introduction: Uncontrolled results suggest that diaphragmatic breathing (DB) is effective in gastroesophageal reflux disease (GERD) but the mechanism of action and rigor of proof is lacking. This study aimed to determine the effects of DB on reflux, lower esophageal sphincter (LES), and gastric pressures in patients with upright GERD and controls.
Methods: Adult patients with pH proven upright GERD were studied. During a high-resolution impedance manometry, study patients received a standardized pH neutral refluxogenic meal followed by LES challenge maneuvers (Valsalva and abdominal hollowing) while randomized to DB or sham. After that, patients underwent 48 hours of pH-impedance monitoring, with 50% randomization to postprandial DB during the second day.
Results: On examining 23 patients and 10 controls, postprandial gastric pressure was found to be significantly higher in patients compared with that in controls (12 vs 7 mm Hg, $P = 0.018$). Valsalva maneuver produced reflux in 65.2% of patients compared with 44.4% of controls ($P = 0.035$). LES increased during the inspiratory portion of DB (42.2 vs 23.1 mm Hg, $P < 0.001$) in patients and

healthy persons. Postprandial DB reduced the number of postprandial reflux events in patients (0.36 vs 2.60, P < 0.001) and healthy subjects (0.00 vs 1.75, P < 0.001) compared with observation. During 48-hour ambulatory study, DB reduced the reflux episodes on day 2 compared with observation on day 1 in both the patient and control groups (P = 0.049). In patients, comparing DB with sham, total acid exposure on day 2 was not different (10.2 ± 7.9 vs 9.4 ± 6.2, P = 0.804). In patients randomized to DB, esophageal acid exposure in a 2-hour window after the standardized meal on day 1 vs day 2 reduced from 11.8% ±6.4 to 5.2% ± 5.1, P = 0.015.
Discussion: In patients with upright GERD, DB reduces the number of postprandial reflux events pressure by increasing the difference between LES and gastric pressure. These data further encourage studying DB as therapy for GERD.
Reference: Effects of Diaphragmatic Breathing on the Pathophysiology and Treatment of Upright Gastroesophageal Reflux: A Randomized Controlled Trial. Am J Gastroenterol 2021 Jan 1;116(1):86-94.

#14 PPIs for persistent throat symptoms = not effective

Objective: To assess the use of proton pump inhibitors (PPIs) to treat persistent throat symptoms.
Design: Pragmatic, double blind, placebo controlled, randomised trial.
Setting: Eight ear, nose, and throat outpatient clinics, United Kingdom.
Participants: 346 patients aged 18 years or older with persistent throat symptoms who were randomised according to recruiting centre and baseline severity of symptoms (mild or severe): 172 to lansoprazole and 174 to placebo.
Intervention: Random blinded allocation (1:1) to either 30 mg lansoprazole twice daily or matched placebo twice daily for 16 weeks.
Main outcome measures: Primary outcome was symptomatic response at 16 weeks measured using the total reflux symptom index (RSI) score. Secondary outcomes included symptom response at 12 months, quality of life, and throat appearances.
Results: Of 1427 patients initially screened for eligibility, 346 were recruited. The mean age of the study sample was 52.2 (SD 13.7) years, 196 (57%) were women, and 162 (47%) had severe symptoms at presentation; these characteristics were balanced across treatment arms. The primary analysis was performed on 220 patients who completed the primary outcome measure within a window of 14-20 weeks. Mean RSI scores were similar between treatment arms at baseline: lansoprazole 22.0 (95% confidence interval 20.4 to 23.6) and placebo 21.7 (20.5 to 23.0). Improvements (reduction in RSI score) were observed in both groups-score at 16 weeks: lansoprazole 17.4 (15.5 to19.4) and placebo 15.6 (13.8 to 17.3). No statistically significant difference was found between the treatment arms: estimated difference 1.9 points (95% confidence interval -0.3 to 4.2 points; P=0.096) adjusted for site and baseline symptom severity. Lansoprazole showed no benefits over placebo for any secondary outcome measure, including RSI scores at 12 months: lansoprazole 16.0 (13.6 to 18.4) and placebo 13.6 (11.7 to 15.5): estimated difference 2.4 points (-0.6 to 5.4 points).
Conclusions: No evidence was found of benefit from PPI treatment in patients with persistent throat symptoms. RSI scores were similar between the lansoprazole and placebo groups after 16 weeks of treatment and at the 12 month follow-up.
Reference: Use of proton pump inhibitors to treat persistent throat symptoms: multicentre, double blind, randomised, placebo controlled trial. BMJ. 2021 Jan 7;372:m4903.

Eosinophilic esophagitis (EoE)

Clinical Features

- Adults:
  - Dysphagia = predominant symptom (including food bolus impaction)
  - Heartburn uncommon
  - Sx present for ~ 3 years before dx
  - Predominantly males & high rate of atopy present
- Kids
  - Feeding dysfunction
  - Failure to thrive
  - Abdominal pain
  - Vomiting/regurgitation/reflux
  - High rate of atopy present
  - Long duration of symptoms prior to diagnosis,

EGD:

- Esophageal changes: exudates, rings, edema, furrows, strictures, narrowing, and crêpe-paper mucosa
- Only a minority have an endoscopically normal-appearing esophagus.

Histology

- Esophageal eosinophilia ≥15 eos/hpf (approximately 60 eos/mm2)

Prognosis

- Natural history = chronic.

- EoE can progresses from inflammatory-predominant to a fibrostenotic predominant disease.

Rx:

- Moreover, there is no current known cure.
- It is exceedingly rare for children to “grow out of” EoE.
- Topical steroids and esophageal dilation.
- Multiple clinical trials of fluticasone and budesonide have clearly demonstrated efficacy
- Swallowed/topical steroids are now considered a first-line treatment for EoE
- Dietary elimination has been added with the recognition that EoE is often a food antigen-driven process
- which removed dairy, wheat, egg, soy, nuts, and seafood
- esophageal dilation is an important therapeutic option for EoE that addresses the fibrostenotic aspects of the disease,

Reference: Red Between the Lines: Evolution of Eosinophilic Esophagitis as a Distinct Clinicopathologic Syndrome. Dig Dis Sci. 2020 Dec;65(12):3434-3447

#15 Topical oral corticosteroids > placebo in EoE remission in adults

Background & aims: Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder. Swallowed topical-acting corticosteroids are effective in bringing active EoE into remission. However, it is not clear whether these drugs are effective for long-term maintenance of remission.
Methods: We performed a double-blind trial to compare the efficacy and safety of 2 dosages of a budesonide orodispersible tablet (BOT) vs placebo in maintaining remission of EoE. Maintenance of remission was defined as absence of clinical and histologic relapse and no premature withdrawal for any reason. Two hundred and four adults with EoE in clinical and histologic remission, from 29 European study sites, were randomly assigned to groups given BOT 0.5 mg twice daily (n = 68), BOT 1.0 mg twice daily (n = 68), or placebo twice daily (n = 68) for up to 48 weeks.
Results: At end of treatment, 73.5% of patients receiving BOT 0.5 mg twice daily and 75% receiving BOT 1.0 mg twice daily were in persistent remission compared with 4.4% of patients in the placebo group (P < .001 for both comparisons of BOT with placebo). Median time to relapse in the placebo group was 87 days. The frequency of adverse events was similar in the BOT and placebo groups. Morning serum levels of cortisol were in the normal range at baseline and did not significantly change during treatment. Four patients receiving BOT developed asymptomatic, low serum levels of cortisol. Clinically manifested candidiasis was suspected in 16.2% of patients in the BOT 0.5 mg group and in 11.8% of patients in the BOT 1.0 mg group; all infections resolved with treatment.
Conclusions: In a phase 3 trial, up to 48 weeks of treatment with BOT (0.5 mg or 1.0 mg twice daily) was superior to placebo in maintaining remission of EoE. Both dosages were equally effective and well tolerated. EudraCT number; 2014-001485-99; ClinicalTrials.gov number, NCT02434029.
Reference: Budesonide Orodispersible Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With Eosinophilic Esophagitis. Gastroenterology. 2020 Nov;159(5):1672-1685.e5

#16 Topical oral corticosteroids > placebo in EoE remission in children

Context: Treatment of eosinophilic esophagitis (EoE) is focused on dietary, pharmacologic, and endoscopic therapy options. Within the pharmacologic alternatives, topical corticosteroids are the most used, and a large number of studies evaluating their effectiveness have been published, requiring a new summary of evidence.
Objective: To evaluate the histologic and clinical effectiveness of using corticosteroids in pediatric patients with a diagnosis of EoE.
Data sources: Cochrane Central Register of Controlled Trials, Medline, Embase, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, Latin American and Caribbean Health Sciences Literature, and ClinicalTrials.gov (June 2019).
Study selection: We selected randomized controlled trials assessing corticosteroids versus a placebo or dietary treatment of EoE in children.
Data extraction: Methodologic quality of evidence was evaluated by using the Cochrane Collaboration's risk of bias tool and the Grading of Recommendations Assessment, Development, and Evaluation system. The primary outcomes were clinical and histologic improvement.
Results: A total of 1655 studies were identified. Five studies were included (206 patients). Histologic response was 49.25% in the corticosteroids group and 4.16% in the placebo group (risk ratio 11.05 [confidence interval 3.8-32.15]; P < .0001). Symptomatic response was 33.6% in the corticosteroids group and 21.8% in the control group (risk ratio 1.62 [confidence interval 0.94-2.79]; P = .08). There were no major adverse effects.
Limitations: Heterogeneity of the diagnosis of EoE.
Conclusions: Our review revealed favorable results of corticosteroids versus placebo, mainly in histologic response. More studies are needed, by using validated clinical scores, to obtain more reliable results.
Reference: Corticosteroids for Eosinophilic Esophagitis in Children: A Meta-analysis. Pediatrics. 2020 Nov;146(5):e20200874.

Bottom Lines

- H pylori is the major risk factor for gastric cancer
- All H pylori infections should be considered pathogenic and should be eradicated
- Test for eradication success for HP
- Antibiotic resistance for HP exists
- HP infection is linked to ITP, B12 & Iron deficiency and chronic urticaria
- HOB elevation in patients with nocturnal GERD is effective
- Empiric PP treatment for patient with non specific throast sympoms is not
- Consider eosinophilic esophagitis (EoE) in adults with dysphage (esp food bolus impaction) and in kids with failure to thrive
- Topical swallowed corticosteroids are effective in treating EoE in children and adults

APPENDIX

#1: PubMed: Kyoto global consensus report on Helicobacter pylori gastritis.

OBJECTIVE: To present results of the Kyoto Global Consensus Meeting, which was convened to develop global consensus on (1) classification of chronic gastritis and duodenitis, (2) clinical distinction of dyspepsia caused by Helicobacter pylori from functional dyspepsia, (3) appropriate diagnostic assessment of gastritis and (4) when, whom and how to treat H. pylori gastritis.
DESIGN: Twenty-three clinical questions addressing the above-mentioned four domains were drafted for which expert panels were asked to formulate relevant statements. A Delphi method using an anonymous electronic system was adopted to develop the consensus, the level of which was predefined as ≥80%. Final modifications of clinical questions and consensus were achieved at the face-to-face meeting in Kyoto.
RESULTS: All 24 statements for 22 clinical questions after extensive modifications and omission of one clinical question were achieved with a consensus level of >80%. To better organize classification of gastritis and duodenitis based on aetiology, a new classification of gastritis and duodenitis is recommended for the 11th international classification. A new category of H.pylori-associated dyspepsia together with a diagnostic algorithm was proposed. The adoption of grading systems for gastric cancer risk stratification, and modern image-enhancing endoscopy for the diagnosis of gastritis, were recommended. Treatment to eradicate H. pylori infection before preneoplastic changes develop, if feasible, was recommended to minimize the risk of more serious complications of the infection.
CONCLUSIONS: A global consensus for gastritis was developed for the first time, which will be the basis for an international classification system and for further research on the subject.
REFERENCES: *Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015 Sep;64(9):1353-67.*

#2 Maastricht V/Florence Report: Management of Helicobacter pylori Infection

Important progress has been made in the management of Helicobacter pylori infection and in this fifth edition of the Maastricht Consensus Report, key aspects related to the clinical role of H. pylori were re-evaluated in 2015. In the Maastricht V/Florence Consensus Conference, 43 experts from 24 countries examined new data related to H. pylori in five subdivided workshops: (1) Indications/Associations, (2) Diagnosis, (3) Treatment, (4) Prevention/Public Health, (5) H. pylori and the Gastric Microbiota. The results of the individual workshops were presented to a final consensus voting that included all participants. Recommendations are provided on the basis of the best available evidence and relevance to the management of H. pylori infection in the various clinical scenarios.
Reference: *Malfertheiner P et al for the European Helicobacter and Microbiota Study Group and Consensus panel.Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut. 2017 Jan;66(1):6-30.*

#3 ACG Clinical Guideline: Treatment of Helicobacter pylori Infection

Helicobacter pylori (H. pylori) infection is a common worldwide infection that is an important cause of peptic ulcer disease and gastric cancer. H. pylori may also have a role in uninvestigated and functional dyspepsia, ulcer risk in patients taking low-dose aspirin or starting therapy with a non-steroidal anti-inflammatory medication, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura. While choosing a treatment regimen for H. pylori, patients should be asked about previous antibiotic exposure and this information should be incorporated into the decision-making process. For first-line treatment, clarithromycin triple therapy should be confined to patients with no previous history of macrolide exposure who reside in areas where clarithromycin resistance amongst H. pylori isolates is known to be low. Most patients will be better served by first-line treatment with bismuth quadruple therapy or concomitant therapy consisting of a PPI, clarithromycin, amoxicillin, and metronidazole. When first-line therapy fails, a salvage regimen should avoid antibiotics that were previously used. If a patient received a first-line treatment containing clarithromycin, bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options. If a patient received first-line bismuth quadruple therapy, clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options. Details regarding the drugs, doses and durations of the recommended and suggested first-line and salvage regimens can be found in the guideline.
Reference*: Chey WD et al. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol. 2017 Feb;112(2):212-239.*

#4 Taipei Global Consensus

Objective: A global consensus meeting was held to review current evidence and knowledge gaps and propose collaborative studies on population-wide screening and eradication of *Helicobacter pylori* for prevention of gastric cancer (GC).
Methods: 28 experts from 11 countries reviewed the evidence and modified the statements using the Delphi method, with consensus level predefined as ≥80% of agreement on each statement. The Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach was followed.
Results: Consensus was reached in 26 statements. At an individual level, eradication of *H. pylori* reduces the risk of GC in asymptomatic subjects and is recommended unless there are competing considerations. In cohorts of vulnerable subjects (eg, first-degree relatives of patients with GC), a screen-and-treat strategy is also beneficial. *H. pylori* eradication in patients with early GC after curative endoscopic resection reduces the risk of metachronous cancer and calls for a re-examination on the hypothesis of 'the point of no return'. At the general population level, the strategy of screen-and-treat for *H. pylori* infection is most cost-effective in young adults in regions with a high incidence of GC and is recommended preferably before the development of atrophic gastritis and intestinal metaplasia. However, such a strategy may still be effective in people aged over 50, and may be integrated or included into national healthcare priorities, such as colorectal cancer screening programmes, to optimise the resources. Reliable locally effective regimens based on the principles of antibiotic stewardship are recommended. Subjects at higher risk of GC, such as those with advanced gastric atrophy or intestinal metaplasia, should receive surveillance endoscopy after eradication of *H. pylori*.

Conclusion: Evidence supports the proposal that eradication therapy should be offered to all individuals infected with *H. pylori*. Vulnerable subjects should be tested, and treated if the test is positive. Mass screening and eradication of *H. pylori* should be considered in populations at higher risk of GC.
Reference: Screening and eradication of Helicobacter pylori for gastric cancer prevention: the Taipei global consensus. Gut. 2020 Dec;69(12):2093-2112

Other H Pylori References:

- Colin H et al. Recent Developments Pertaining to H. pylori Infection. American Journal of Gastroenterology. January 2021, Volume 116 (1), p 1–3
- The prevention of gastric cancer by Helicobacter pylori eradication. The prevention of gastric cancer by Helicobacter pylori eradication. Curr Opin Gastroenterol. 2021 Nov 1;37(6):625-630.

GERD

Highlights of these guidelines that are relevant for primary care include:

Assessment

- Endoscopy is the first test for evaluation of patients presenting with dysphagia or other alarm symptoms (weight loss and GI bleeding) and for patients with multiple risk factors for Barrett's esophagus.
- In patients for whom the diagnosis of GERD is suspected but not clear, and endoscopy shows no objective evidence of GERD, we recommend reflux monitoring be performed off therapy to establish the diagnosis

GERD Management

- Weight loss in overweight & obese patients improves GERD symptoms.
- Avoid meals within 2–3 hr of bedtime & avoid trigger foods
- Elevate head of bed for nighttime GERD symptoms.
- For patients with classic GERD symptoms & no alarm symptoms, start an 8-wk trial of empiric PPIs once daily before a meal.
- Take PPIs 30–60 min before a meal rather than at bedtime for GERD symptom control.
- Attempt to discontinue PPIs in patients whose symptoms respond to an 8-wk empiric trial of PPIs.
- For patients with GERD who require maintenance therapy with PPIs, the PPIs should be administered in the lowest dose that effectively controls GERD symptoms and maintains healing of reflux esophagitis.
- We recommend against routine addition of medical therapies in PPI nonresponders.
- We recommend maintenance PPI therapy indefinitely or antireflux surgery for patients with LA grade C or D esophagitis.
- Do not use baclofen or a prokinetic agent. Only use sucralfate for GERD in pregnancy
- We suggest on-demand/or intermittent PPI therapy for heartburn symptom control in patients with NERD.

Objectives: At the end of this session, the participant will be able to:

- describe recent studies on managing persons with sleep disturbances
- describe the management of persons with concussion
- describe the management of children with seizure disorders

This topic is a veritable *potpourri* that includes studies from the last 3 years and addresses, among other things, sleep disturbances other than sleep apnea, concussion, and seizure disorders in children. This year, other separate topics include dementia/delirium and headaches.

Sleep disturbances

Medications to improve sleep have been generally disappointing – limited effectiveness and increased harms. The next few studies address what other approaches are effective.

1. Guidelines for obstructive sleep apnea and insomnia from the US DoD and Veteran Affairs

Clinical question: How should presumed obstructive sleep apnea or chronic insomnia be diagnosed and managed?
Study design: Practice guideline **Funding source:** Government
Synopsis: This working group, which represented a wide range of stakeholders, based their 41 recommendations on a systematic search and analysis of existing research. Only one member of the group (who was the lead author) had a financial conflict of interest. They focused on outcomes of importance to patients. The research quality was graded, and the recommendations labeled with the quality of the evidence. Here is a broad and incomplete synopsis of their recommendations: To diagnose OSA and insomnia: (1) Consider assessing for sleep disorder in patients with cardiovascular and cerebrovascular events, heart failure, and long-term opioid use (weak evidence) (2) Begin with the STOP questions (Snoring/Tiredness/Observed stopped breathing/blood Pressure); they are easier to answer and provide similar accuracy as the STOP-BANG questions (which adds Body mass index, Age, Neck size, and Gender) (weak evidence) (3) Test at home for OSA first, followed by repeat home testing or laboratory testing if nondiagnostic (strong evidence) Management of OSA: (1) Positive airway pressure is the primary treatment for OSA (strong evidence) (2) Do not use oxygen therapy (weak against) Management of chronic insomnia: (1) Sleep hygiene education should not be used alone for insomnia (weak evidence) (2) Consider cognitive behavioral therapy (strong evidence) or brief behavioral therapy (weak evidence) (3) Consider auricular acupuncture (weak evidence) (4) If considering pharmacotherapy, consider short-term, low-dose doxepin or a nonbenzodiazepine such as zolpidem; do not use benzodiazepines or trazodone (weak evidence) (5) Avoid diphenhydramine, melatonin, valerian, chamomile (weak evidence), and kava (strong evidence)
Bottom line: Obstructive sleep apnea (OSA) can be identified using the STOP questions (see the synopsis) and confirmed in most people using at-home testing. Positive airway pressure is the mainstay of OSA. For chronic insomnia, avoid medications; use cognitive behavioral therapy, brief behavioral therapy, or auricular acupuncture using seeds (ask an acupuncturist for a description) instead. Medicines can be used in the short term but should be limited to doxepin or nonbenzodiazepine receptor agonists such as zolpidem (Ambien). The complete guideline, which includes an algorithm, can be found at https://bit.ly/3atD31b.
Mysliwiec V, Martin J, Ulmer CS, et al. The management of chronic insomnia disorder and obstructive sleep apnea: Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guidelines. Ann Intern Med 2020;172(5):325-336. doi:10.7326/M19-3575

2. Telephone-based cognitive behavioral therapy for insomnia is effective

Clinical question: Can cognitive behavioral therapy for insomnia in patients with chronic pain be effectively delivered via telephone?
Study design: Randomized controlled trial (nonblinded) **Funding source:** Industry + foundation
Synopsis: These researchers recruited 327 participants with moderate to severe osteoarthritis and clinical insomnia identified via telephone screening. In other words, the patients hadn't sought care, but were screened positive for insomnia with an average score on the Insomnia Severity Index of 15.5 of a possible 28. Most (75%) were women, most were white (96%), and almost half (48%) were college graduates. The patients were randomized (allocation concealment unknown) to receive telephone-based CBT-I (focused on in-bed restriction, cognitive strategies to reduce hyperarousal, and setting realistic sleep expectations) or an education-only intervention. All participants were contacted 6 times by telephone over 8 weeks. Two months after the end of the treatment period, insomnia scores decreased by 8.1 points in the CBT-I group and 4.8 points in the education-only group (P = .001); 81% of the CBT-I group had at least a 30% improvement in insomnia score as compared with 49% of the education group (P <.001). Differences in scores were maintained 12 months after treatment. Feelings of fatigue similarly improved to a greater extent with CBT-I.
Bottom line: In patients with clinical insomnia and chronic pain, cognitive behavioral therapy for insomnia (CBT-I) delivered via telephone over 6 sessions leads to relief of sleeplessness that is sustained for at least a year. In this study, general education also provided insomnia relief to many patients.
McCurry SM, Zhu W, Von Korff M, et al. Effect of telephone cognitive behavioral therapy for insomnia in older adults with osteoarthritis pain. A randomized clinical trial. JAMA Intern Med 2021;181(4):530-538.

3. Limited data suggest that music improves sleep quality in older adults

Clinical question: Does music improve sleep quality in older adults?
Study design: Meta-analysis (randomized controlled trials) **Funding source:** Self-funded or unfunded

Synopsis: This team of authors searched several databases and registries to identify English-language or Chinese-language publications of randomized trials of music to improve sleep in adults 60 years and older. They excluded studies that evaluated persons with cognitive dysfunction and those with impaired hearing. The team used the Cochrane Collaboration tool to assess the risk of bias of the included studies, and ultimately included 5 small trials with 288 total patients, all from community settings. The music interventions included a wide range of live and recorded music, 30 to 60 minutes long, and the intervention periods ranged from 2 days to 3 months. The primary outcome measure was the Pittsburgh Sleep Quality Index (range: 0 to 21; scores higher than 5 indicate poor sleep quality; McDonnell and colleagues report the minimum clinically important difference is 3.0). In general, the studies were of mixed quality. Overall, music modestly improved sleep quality more than no music (mean difference [MD] –1.96; 95% CI –3.23 to –0.69), but there was heterogeneity in the data. Sedative music (slow tempo, soft volume, smooth melody) was more effective than rhythmic music (MD –2.35; –3.59 to –1.10 vs MD −0.25; −2.23 to 1.73, respectively). Finally, studies that were longer than 4 weeks found greater improvements than shorter studies (MD −2.61; −4.72 to −0.50 vs −2.00; −3.99 to −0.00). On average, none of the studies resulted in clinically important improvements. The authors do not report adverse events.
Bottom line: This study, in which the underlying data are limited and of mixed quality, suggests that listening to music, especially sedative music, can improve sleep quality in older adults.
Chen CT, Tung HH, Fang CJ, et al. Effect of music therapy on improving sleep quality in older adults: A systematic review and meta-analysis. J Am Geriatr Soc 2021;69(7):1925-1932.

4. Medications for daytime sleepiness in individuals with idiopathic hypersomnia

Background: Idiopathic hypersomnia is a disorder of excessive daytime sleepiness, often accompanied by long sleep times or pronounced difficulty in awakening, in the absence of a known cause. The optimal treatment strategy for idiopathic hypersomnia is currently unknown.
Objectives: To assess the effects of medications for daytime sleepiness and related symptoms in individuals with idiopathic hypersomnia and, in particular, whether medications may: 1. reduce subjective measures of sleepiness; 2. reduce objective measures of sleepiness; 3. reduce symptoms of cognitive dysfunction; 4. improve quality of life; and 5. be associated with adverse events.
Search methods: We searched the following databases on 4 February 2021: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to 1 February 2021), and reference lists of articles. CRS Web includes randomized or quasi-randomized controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialized registers of Cochrane Review Groups, including the Cochrane Epilepsy Group. We previously searched the WHO ICTRP separately when loading of ICTRP records into CRS Web was temporarily suspended. **Selection criteria:** Randomized studies comparing any medication to placebo, another medication, or a behavioral intervention. **Data collection and analysis:** Two review authors independently extracted data and assessed trial quality. We contacted study authors for additional data. We collected data on adverse events from the included trials.
Main results: We included three trials, with a total of 112 participants. Risk of bias was low for the included studies. Two pharmaceutical company-sponsored trials compared modafinil with placebo, involving 102 participants, nearly all of whom had idiopathic hypersomnia without long sleep time. Modafinil significantly improved self-reported sleepiness on the Epworth Sleepiness Scale by 5.08 points more than placebo (95% confidence interval (CI) 3.01 to 7.16; 2 studies, 101 participants; high-certainty evidence). Modafinil also significantly improved disease severity on the Clinical Global Impression of Severity scale by 1.02 points (95% CI 0.11 to 1.93; 1 study, 30 participants; moderate-certainty evidence) and resulted in a greater proportion of participants who were "much improved" or "very much improved" on the Clinical Global Impression of Change (odds ratio (OR) for improvement 5.14, 95% CI 1.76 to 15.00; 1 study, 70 participants; moderate-certainty evidence). Ability to remain awake on the Maintenance of Wakefulness Test was significantly improved with modafinil, by 4.74 minutes more than with placebo (95% CI 2.46 to 7.01; 2 studies, 99 participants; high-certainty evidence). Ratings of exhaustion and effectiveness/performance were improved with modafinil compared to placebo in one study. Number of naps per week was no different between modafinil and placebo across two studies. Participants receiving modafinil experienced more side effects, although the difference did not reach statistical significance (OR 1.68, 95% CI 0.28 to 9.94; 2 studies, 102 participants; low-certainty evidence).
One trial studying 20 participants with different disorders of sleepiness included 10 participants with idiopathic hypersomnia, with or without long sleep time, and compared clarithromycin to placebo. We only included the subset of trial data for those participants with idiopathic hypersomnia, per our protocol. There were no significant differences between clarithromycin and placebo for the Epworth Sleepiness Scale, psychomotor vigilance testing, sleep inertia, other subjective ratings, or side effects.
Authors' conclusions: Modafinil is effective for the treatment of several aspects of idiopathic hypersomnia symptomatology, based on studies predominantly including participants with idiopathic hypersomnia without long sleep times, with low risk of bias, and evidence certainty ranging from high to low. There is insufficient evidence to conclude whether clarithromycin is effective for the treatment of idiopathic hypersomnia. There is a clear need for additional studies testing interventions for the treatment of idiopathic hypersomnia.
Trotti LM, Becker LA, Friederich Murray C, Hoque R. Medications for daytime sleepiness in individuals with idiopathic hypersomnia. Cochrane Database of Systematic Reviews 2021, Issue 5. Art. No.: CD012714. DOI: 10.1002/14651858.CD012714.pub2.

Concussion

This next study comes right out of the medical journal, *Duh*.

5. Failure to wear a helmet while motorcycling is bad for your head

Clinical question: Do helmets reduce serious injury and fatalities among motorcyclists?
Study design: Cross-sectional **Funding source:** Unknown/not stated
Synopsis: Many studies regarding mandatory helmet laws for motorcyclists have examined pre-law and post-law data. This study takes advantage of a natural experiment going on at the Tennessee-Virginia-Kentucky border, in which Kentucky is the only state of the 3 without a law mandating helmet use for all motorcycle riders. At a Level I trauma center serving the 3 states, these researchers

identified all 729 motorcycle crash victims admitted to the center between mid-2005 and mid-2015. Among the Kentucky motorcyclists, 41% were wearing helmets, compared with 89% in Tennessee and 81% in Virginia. Compared with motorcyclists in the 2 other states, those in Kentucky had a higher in-hospital fatality rate (7.3% vs 4.3%; P < .001), as well as significantly longer lengths of stay, more severe head and neck injuries, and more surgeries. Not surprisingly, unhelmeted status across all 3 states predicted strikingly more severe head injuries and death (adjusted odds ratios 15.3 and 4.2, respectively). Note that this was a cohort of crash victims who survived long enough to be admitted. Unhelmeted heads were likely even more prevalent among those who died in the crash.
Bottom line: In a medical center serving 3 neighboring states, motorcycle crash victims from the 2 states with universal helmet laws (Tennessee and Virginia) had significantly lower rates of death and severe head/neck injuries than the state without such a law (Kentucky). The motorcyclists who died in Kentucky were younger than those in Tennessee and Virginia, and included more women.
Testerman GM, Prior DC, Wells TD, et al. Helmets matter: Kentucky motorcycle crash victims seen at a Tennessee trauma center. South Med J 2018;111(1):8-11.

Clinical scores can be helpful in identifying who needs urgent imaging after head injury. The PECARN, CHALICE and CATCH (https://www.essentialevidenceplus.com/content/poem/190803) have all been found to be accurate in children. A modification of the CATCH, the CATCH2 looks pretty good, too.

6. CATCH2 score accurate to identify children with minor head injury who need CT

Clinical question: Which children with minor head injury can safely avoid computed tomography of the head?
Study design: Cohort (prospective) **Funding source:** Government **Setting:** Emergency department
Synopsis: These same investigators had previously developed the CATCH score to identify children with minor head injury who potentially benefitted from a head CT. It was a simple checklist of 7 items; if any of the first 4 were present, the child was at high risk for neurosurgical intervention, and if any of the final 3 were present, they were at medium risk for brain injury on CT. The 7 items are: (1) a Glasgow Coma Scale (GCS) score of less than 15 at 2 hours after injury; (2) suspected open or depressed skull fracture; (3) history of worsening headache; (4) irritability on examination; (5) any sign of basal skull fracture; (6) a large, boggy hematoma of the scalp; and (7) dangerous mechanism of injury including motor vehicle accident, a fall from 3 or more feet or down 5 or more stairs, or a bicycle injury without a helmet. (Personal aside: Wear your helmets, people!) The rule was originally developed in 3866 children with a GCS score of 13 to 15 accompanied by loss of consciousness, amnesia, disorientation, persistent vomiting, or irritability; the current study prospectively applied it to 4494 children (434 were subsequently lost to follow-up). The kids ranged in age from 1 month to 16 years, with only 11% younger than 2 years and 9% with a GCS score of 13 or 14. Physicians used their clinical judgment in ordering CT and were told not to use the CATCH score. Ultimately, 35% of patients underwent CT and the rest had 2 weeks of clinical follow-up to determine their outcome. Overall, 4.9% (n = 197) had brain injury on CT and 0.6% (n = 23) underwent a neurosurgical intervention. The CATCH score correctly identified 21 of 23 children needing neurosurgical intervention, and 192 of 197 with brain injury on CT. Adding an eighth criterion (4 or more episodes of vomiting), which they now call the CATCH2 rule, identified all 23 children requiring neurosurgical intervention and 196 of 197 with brain injury on CT. However, it hurt the specificity, decreasing it from approximately 58% to approximately 47%.
Bottom line: Avoiding unnecessary head computed tomography (CT) is important, given the radiosensitivity of a child's brain. If we strictly follow the Canadian Assessment of Tomography for Childhood Head injury (CATCH) score as a guide to ordering CT, though, approximately 55% of children with minor head injury would have a head CT, compared with only 35% when physicians use their clinical judgment. Rules like this should serve as a check on the decision-making of experienced clinicians, and as a guide for learners.
Osmond MH, Klassen TP, Wells GA, et al, for the Pediatric Emergency Research Canada (PERC) Head Injury Study Group. Validation and refinement of a clinical decision rule for the use of computed tomography in children with minor head injury in the emergency department. CMAJ 2018;190(27):E816-E822.

	CATCH				CATCH2			
	Se	**Sp**	**LR+**	**LR-**	**Se**	**Sp**	**LR+**	**LR-**
Brain Injury on CT	97.5	59.6	2.4	0.04	99.5	47.8	1.9	0.01
Neurosurgery	91.3	57.1	2.1	0.2	100	45.7	1.8	0

The next papers address how to assist those with concussion to return to pre-injury activities.

7. Return to play guidelines following concussion

The following summarizes the return to play guidelines based on a consensus statement at the 5th International Conference on Concussion in Sport.

1. 24-48 hours of physical and cognitive rest.
2. Symptom limited activity.
3. Light aerobic exercise, no resistance training.
4. Sport-specific exercise.
5. Noncontact training drills.
6. Full contact training after medical clearance.

7. Game play.

If any postconcussion symptoms occur during the above progression, the athlete should drop back to the previous level and try to progress again after 24 hours.

McCrory P, Meeuwisse W, Dvořák J, et al. Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med 2017;51:838–847.

8. After concussion, early subthreshold aerobic exercise returns teens to play sooner than stretching

Clinical question: Do adolescents with a recent sports-related concussion who engage in daily subthreshold aerobic exercise recover sooner than those who participate in a daily stretching program?

Study design: Randomized controlled trial (single-blinded) **Funding source:** Government

Synopsis: These researchers randomized adolescents between 13 and 18 years of age with a sports-related concussion in the preceding 10 days to participate in a daily aerobic exercise program (n = 52) or a daily placebo-like stretching program (n = 51). The researchers excluded teens with focal deficits, the inability to exercise for reasons other than concussion, a Glasgow Coma Scale score of 12 or less, more than 3 prior concussions, a concurrent second head injury before enrollment, a baseline score of 5 points or less on a postconcussion symptom scale, an ability to tolerate maximal exercise without symptoms at the baseline visit, and those taking psychotropic medications. Once the diagnosis of concussion was confirmed, each participant underwent an exercise tolerance test to the point of developing concussion symptoms, at which point they were asked to rate the symptom severity. The teens randomized to do aerobic exercise were instructed not to stretch but to exercise for up to 20 minutes on an exercise bike or treadmill with a target heart rate of 80% of the point of symptom exacerbation at baseline. They were instructed to stop exercising if their symptoms increased by 2 or more points from their baseline. The control patients were given a booklet containing a 20-minute gentle, whole-body stretching program that would not elevate the heart rate. The main outcome was time to recovery, defined as lack of symptoms confirmed by a normal physical examination (including vestibular and oculomotor) and the ability to exercise to exhaustion without exacerbation concussion symptoms. Although neither the research assistants nor the participants were masked to exercise allocation, the treating physicians who made the clinical recovery determination were masked. The median time to recovery was 13 days in the teens treated with exercise compared with 17 days for the control patients. Additionally, the exercise group was less likely to have delayed recovery, although this was not statistically significant and likely reflects an inadequate sample size.

Bottom line: Adolescents with recent sports-related concussion who participate in an individualized aerobic exercise program for 20 minutes a day recover faster than those who participate in a low-level stretching program.

Leddy JJ, Haider MN, Ellis MJ, et al. Early subthreshold aerobic exercise for sport-related concussion: a randomized clinical trial. JAMA Pediatr 2019;173(4):319-325.

9. Avoiding video screens for 48 hours after a head injury decreases concussion recovery time

Clinical question: Does avoiding screen time after an acute head injury decrease concussion recovery time?

Study design: Randomized controlled trial (nonblinded) **Funding source:** Unknown/not stated

Synopsis

These investigators recruited 125 persons, aged 12 to 25 years, who presented to an emergency department at a tertiary care center within 24 hours of an acute concussion. The participants had a Glasgow Coma Score of 15 and no intracranial abnormalities on imaging. They were randomized into 2 groups and asked to avoid the use of video screens for 48 hours (intervention; n = 59) or not to avoid video screens (control; n = 66). All participants completed the Post-Concussive Symptom Scale (PCSS) daily for the 10 days after enrollment. Although the PCSS is a validated research scale, it is not widely used in sports medicine clinics. It includes 22 items, each rated from 0 to 6 points (range = 0 - 132). A higher score indicates more severe symptoms. The main outcome of the study was time to recovery, defined by a PCSS score of 3 or less. Overall, 30 participants (a troubling 24%) did not complete the study; the dropout rate was the same in each group. The authors don't report the number of participants who recovered, but information buried in a graph indicates that 21 of the 53 (60.4%) persons in the control group who had complete data recovered compared with 14 of 50 (72.0%) persons in the intervention group (hazard ratio [HR] 0.51; 95% CI 0.29 - 0.90). The women in the intervention group were less likely to recover than the men in the intervention group (HR 0.34; 0.19 - 0.60). Finally, among those who recovered, persons in the control group took longer to recover than persons in the intervention group (8.0 vs 3.5 days, respectively).

Bottom line: In this study, avoiding video screens modestly increased the proportion of persons with concussion who recover and shortened the duration of symptoms.

Macnow T, Curran T, Tolliday C, et al. Effect of screen time on recovery from concussion: a randomized clinical trial. JAMA Pediatr 2021;175(11):1124-1131.

Seizure disorders in children

While many children with seizure disorders are co-managed with neurologists, front-line clinicians often have to manage emergency situations.

10. Levetiracetam is comparable to second-line agents to treat children with status epilepticus

Clinical question: Is levetiracetam effective for treating children with convulsive status epilepticus?

Study design: Meta-analysis (randomized controlled trials)

Synopsis: These authors searched several databases and clinical trials registries to identify published and unpublished randomized trials of intravenous levetiracetam for managing convulsive status epilepticus in children aged 1 month to 18 years. The included studies could have used any other treatment. The team used reasonable processes for article selection, quality assessment, and data management. They included 10 studies with 1907 children. Seven of the studies compared levetiracetam with phenytoin and the

remainder used fosphenytoin or valproic acid. Although the included studies had low risks of bias in most areas of concern, 8 of the studies did not mask participants, study personnel, or (understandably) the outcome. In the 7 studies that compared levetiracetam with phenytoin, there was no difference in the rate of the main outcome, cessation of seizures (83% vs 80%), but the data were heterogeneous. Similarly, there was no difference found in the studies using fosphenytoin or valproic acid as comparators. The authors also sliced and diced the data and found no differences in time to cessation of seizure activities, seizure recurrence at 24 hours, need for rapid sequence intubation, need for intensive care, or all-cause mortality. Six of the studies reported adverse events and found no difference between levetiracetam and the other drugs.
Bottom line: Although benzodiazepines remain the first-line treatment of convulsive status epilepticus in children, levetiracetam is comparable with currently recommended second-line agents in effectiveness and adverse effects.
Abdelgadir I, Hamud A, Kadri A, et al. Levetiracetam for convulsive status epilepticus in childhood: systematic review and meta-analysis. Arch Dis Child 2020;106(5):470-476.

11. Two RCTs: levetiracetam is not superior to phenytoin to treat status epilepticus but is easier to use and may be safer

Clinical question: Is levetiracetam superior to phenytoin as a second-line agent in treating children with status epilepticus?
Study design: Randomized controlled trial (nonblinded) **Funding source:** Government **Setting:** Emergency department
Synopsis: Benzodiazepines are first-line treatment for children with status epilepticus, but they only work 40% to 60% of the time. Phenytoin, the currently recommended second-line agent, requires slow administration and can cause hypotension and cardiac arrhythmias. The authors of the 2 studies (one study in the United Kingdom, the other in Australia and New Zealand) used comparable methods: open-label trials of children who presented to emergency departments in status epilepticus needing second-line treatment. The children received either levetiracetam (40 mg/kg over 5 minutes; n [for the 2 studies] = 271) or phenytoin (20 mg/kg over 20 minutes; n = 248). In the EcLiPSE trial, the main outcome was the time to cessation of all seizure activity (similar mean time with levetiracetam and phenytoin: 35 and 45 minutes, respectively), while in ConSEPT the main outcome was whether seizure activity stopped 5 minutes after completing the infusion (again, similar: 60% vs 50%, respectively). In EcLiPSE, one third of patients in each group required an additional anticonvulsant and approximately 20% required rapid sequence induction to halt the seizures. In ConSEPT, however, approximately one quarter of the children in each group required rapid sequence induction. In each study, one child died; each had received phenytoin. In the EcLiPSE trial, one child treated with phenytoin developed life-threatening hypotension, increased focal seizures, and decreased consciousness. ConSEPT reported no other serious events, but it will take a larger study to confidently say that one drug is safer than the other.
Bottom line: These 2 open-label trials show that levetiracetam (Keppra) and phenytoin (Dilantin) are comparable in halting seizures in children with status epilepticus who need second-line treatment. Levetiracetam, however, can be administered more quickly and, according to the very limited data from these trials, it also appears to be safer.
Lyttle MD, Rainford NEA, Gamble C, et al, for the Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019;393(10186):2125-2134.
Dalziel SR, Borland ML, Furyk J, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. *Lancet.* 2019;393(10186):2135-2145.

The prevention of febrile seizures is largely addressed by fever control and, in general, does not include the use of anticonvulsants, as supported by this Cochrane Systematic Review.

12. Prophylactic drug management for febrile seizures in children

Background: Febrile seizures occurring in a child older than one month during an episode of fever affect 2-4% of children in Great Britain and the United States and recur in 30%. Rapid-acting antiepileptics and antipyretics given during subsequent fever episodes have been used to avoid the adverse effects of continuous antiepileptic drugs.
This is an updated version of a Cochrane Review previously published in 2017.
Objectives: To evaluate primarily the effectiveness and safety of antiepileptic and antipyretic drugs used prophylactically to treat children with febrile seizures; and also to evaluate any other drug intervention where there is a sound biological rationale for its use.
Search methods: For the latest update we searched the following databases on 3 February 2020: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to 31 January 2020). CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane Review Groups including the Cochrane Epilepsy Group. We imposed no language restrictions and contacted researchers to identify continuing or unpublished studies. **Selection criteria:** Trials using randomised or quasi-randomised participant allocation that compared the use of antiepileptics, antipyretics or recognised Central Nervous System active agents with each other, placebo, or no treatment. **Data collection and analysis:** For the original review, two review authors independently applied predefined criteria to select trials for inclusion and extracted the predefined relevant data, recording methods for randomisation, blinding, and exclusions. For the 2016 update, a third review author checked all original inclusions, data analyses, and updated the search. For the 2020 update, one review author updated the search and performed the data analysis following a peer-review process with the original review authors. We assessed seizure recurrence at 6, 12, 18, 24, 36, 48 months, and where data were available at age 5 to 6 years along with recorded adverse effects. We evaluated the presence of publication bias using funnel plots.
Main results:
We included 42 articles describing 32 randomised trials, with 4431 randomised participants used in the analysis of this review. We analysed 15 interventions of continuous or intermittent prophylaxis and their control treatments. Methodological quality was moderate to poor in most studies. We found no significant benefit for intermittent phenobarbital, phenytoin, valproate, pyridoxine, ibuprofen, or zinc

sulfate versus placebo or no treatment; nor for diclofenac versus placebo followed by ibuprofen, paracetamol, or placebo; nor for continuous phenobarbital versus diazepam, intermittent rectal diazepam versus intermittent valproate, or oral diazepam versus clobazam.
There was a significant reduction of recurrent febrile seizures with intermittent diazepam versus placebo or no treatment at six months (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.48 to 0.85; 6 studies, 1151 participants; moderate-certainty evidence), 12 months (RR 0.69, 95% CI 0.56 to 0.84; 8 studies, 1416 participants; moderate-certainty evidence), 18 months (RR 0.37, 95% CI 0.23 to 0.60; 1 study, 289 participants; low-certainty evidence), 24 months (RR 0.73, 95% CI 0.56 to 0.95; 4 studies, 739 participants; high-certainty evidence), 36 months (RR 0.58, 95% CI 0.40 to 0.85; 1 study, 139 participants; low-certainty evidence), 48 months (RR 0.36, 95% CI 0.15 to 0.89; 1 study, 110 participants; moderate-certainty evidence), with no benefit at 60 to 72 months (RR 0.08, 95% CI 0.00 to 1.31; 1 study, 60 participants; very low-certainty evidence).
Phenobarbital versus placebo or no treatment reduced seizures at six months (RR 0.59, 95% CI 0.42 to 0.83; 6 studies, 833 participants; moderate-certainty evidence), 12 months (RR 0.54, 95% CI 0.42 to 0.70; 7 studies, 807 participants; low-certainty evidence), and 24 months (RR 0.69, 95% CI 0.53 to 0.89; 3 studies, 533 participants; moderate-certainty evidence), but not at 18 months (RR 0.77, 95% CI 0.56 to 1.05; 2 studies, 264 participants) or 60 to 72 months follow-up (RR 1.50, 95% CI 0.61 to 3.69; 1 study, 60 participants; very low-certainty evidence).
Intermittent clobazam compared to placebo at six months resulted in a RR of 0.36 (95% CI 0.20 to 0.64; 1 study, 60 participants; low-certainty evidence), an effect found against an extremely high (83.3%) recurrence rate in the controls, a result that needs replication.
When compared to intermittent diazepam, intermittent oral melatonin did not significantly reduce seizures at six months (RR 0.45, 95% CI 0.18 to 1.15; 1 study, 60 participants; very-low certainty evidence).
When compared to placebo, intermittent oral levetiracetam significantly reduced recurrent seizures at 12 months (RR 0.27, 95% CI 0.15 to 0.52; 1 study, 115 participants; very low-certainty evidence).
The recording of adverse effects was variable. Two studies reported lower comprehension scores in phenobarbital-treated children. Adverse effects were recorded in up to 30% of children in the phenobarbital-treated groups and 36% in benzodiazepine-treated groups.
We found evidence of publication bias in the meta-analyses of comparisons for phenobarbital versus placebo (seven studies) at 12 months but not at six months (six studies); and valproate versus placebo (four studies) at 12 months. There were too few studies to identify publication bias for the other comparisons.
The methodological quality of most of the included studies was low or very low. Methods of randomisation and allocation concealment often did not meet current standards, and 'treatment versus no treatment' was more commonly seen than 'treatment versus placebo', leading to obvious risks of bias.
Authors' conclusions: We found reduced recurrence rates for intermittent diazepam and continuous phenobarbital, with adverse effects in up to 30% of children. The apparent benefit for clobazam treatment in one trial needs to be replicated. Levetiracetam also shows benefit with a good safety profile; however, further study is required. Given the benign nature of recurrent febrile seizures, and the high prevalence of adverse effects of these drugs, parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management, and, most importantly, the benign nature of the phenomenon.
Offringa M, Newton R, Nevitt SJ, Vraka K. Prophylactic drug management for febrile seizures in children. Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD003031. DOI: 10.1002/14651858.CD003031.pub4.

13. Ketogenic diets for drug-resistant epilepsy

Background: Ketogenic diets (KDs) are high in fat and low in carbohydrates and have been suggested to reduce seizure frequency in people with epilepsy. Such diets may be beneficial for children with drug-resistant epilepsy.
This is an update of a review first published in 2003, and last updated in 2018.
Objectives: To assess the effects of ketogenic diets for people with drug-resistant epilepsy.
Search methods: For this update, we searched the Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid, 1946 to 26 April 2019) on 29 April 2019. The Cochrane Register of Studies includes the Cochrane Epilepsy Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised controlled trials (RCTs) from Embase, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We imposed no language restrictions. We checked the reference lists of retrieved studies for additional relevant studies. **Selection criteria:** RCTs or quasi-RCTs of KDs for people of any age with drug-resistant epilepsy. **Data collection and analysis:** Two review authors independently applied predefined criteria to extract data and evaluated study quality. We assessed the outcomes: seizure freedom, seizure reduction (50% or greater reduction in seizure frequency), adverse effects, cognition and behaviour, quality of life, and attrition rate. We incorporated a meta-analysis. We utilised an intention-to-treat (ITT) population for all primary analyses. We presented the results as risk ratios (RRs) with 95% confidence intervals (CIs).
Main results
We identified 13 studies with 932 participants; 711 children (4 months to 18 years) and 221 adults (16 years and over).
We assessed all 13 studies to be at high risk of performance and detection bias, due to lack of blinding. Assessments varied from low to high risk of bias for all other domains. We rated the evidence for all outcomes as low to very low certainty.
Ketogenic diets versus usual care for children
Seizure freedom (RR 3.16, 95% CI 1.20 to 8.35; P = 0.02; 4 studies, 385 participants; very low-certainty evidence) and seizure reduction (RR 5.80, 95% CI 3.48 to 9.65; P < 0.001; 4 studies, 385 participants; low-certainty evidence) favoured KDs (including: classic KD, medium-chain triglyceride (MCT) KD combined, MCT KD only, simplified modified Atkins diet (MAD) compared to usual care for children. We are not confident that these estimated effects are accurate. The most commonly reported adverse effects were vomiting, constipation and diarrhoea for both the intervention and usual care group, but the true effect could be substantially different (low-certainty evidence).
Ketogenic diet versus usual care for adults
In adults, no participants experienced seizure freedom. Seizure reduction favoured KDs (MAD only) over usual care but, again, we are not confident that the effect estimated is accurate (RR 5.03, 95% CI 0.26 to 97.68; P = 0.29; 2 studies, 141 participants; very low-

certainty evidence). Adults receiving MAD most commonly reported vomiting, constipation and diarrhoea (very low-certainty evidence). One study reported a reduction in body mass index (BMI) plus increased cholesterol in the MAD group. The other reported weight loss. The true effect could be substantially different to that reported.

Ketogenic diet versus ketogenic diet for children

Up to 55% of children achieved seizure freedom with a classical 4:1 KD after three months whilst up to 85% of children achieved seizure reduction (very low-certainty evidence). One trial reported a greater incidence of seizure reduction with gradual-onset KD, as opposed to fasting-onset KD. Up to 25% of children were seizure free with MAD and up to 60% achieved seizure reduction.

Up to 25% of children became seizure free with MAD and up to 60% experienced seizure reduction. One study used a simplified MAD (sMAD) and reported that 15% of children gained seizure freedom rates and 56% achieved seizure reduction. We judged all the evidence described as very low certainty, thus we are very unsure whether the results are accurate.

The most commonly reported adverse effects were vomiting, constipation and diarrhoea (5 studies, very low-certainty evidence). Two studies reported weight loss. One stated that weight loss and gastrointestinal disturbances were more frequent, with 4:1 versus 3:1 KD, whilst one reported no difference in weight loss with 20 mg/d versus 10 mg/d carbohydrates. In one study, there was a higher incidence of hypercalcuria amongst children receiving classic KD compared to MAD. All effects described are unlikely to be accurate.

Ketogenic diet versus ketogenic diet for adults

One study randomised 80 adults (aged 18 years and over) to either MAD plus KetoCal during the first month with MAD alone for the second month, or MAD alone for the first month followed by MAD plus KetoCal for the second month. No adults achieved seizure freedom. More adults achieved seizure reduction at one month with MAD alone (42.5%) compared to MAD plus KetoCal (32.5%), however, by three months only 10% of adults in both groups maintained seizure reduction. The evidence for both outcomes was of very low certainty; we are very uncertain whether the effects are accurate.

Constipation was more frequently reported in the MAD plus KetoCal group (17.5%) compared to the MAD only group (5%) (1 study, very low-certainty evidence). Diarrhoea and increase/change in seizure pattern/semiology were also commonly reported (17.5% to 20% of participants). The true effects of the diets could be substantially different to that reported.

Authors' conclusions

The evidence suggests that KDs could demonstrate effectiveness in children with drug-resistant epilepsy, however, the evidence for the use of KDs in adults remains uncertain. We identified a limited number of studies which all had small sample sizes. Due to the associated risk of bias and imprecision caused by small study populations, the evidence for the use of KDs was of low to very low certainty.

More palatable but related diets, such as the MAD, may have a similar effect on seizure control as the classical KD, but could be associated with fewer adverse effects. This assumption requires more investigation. For people who have drug-resistant epilepsy or who are unsuitable for surgical intervention, KDs remain a valid option. Further research is required, particularly for adults with drug-resistant epilepsy.

Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database of Systematic Reviews 2020, Issue 6. Art. No.: CD001903. DOI: 10.1002/14651858.CD001903.pub5.

14. AAN guideline on withdrawing anti-seizure medications

Clinical question: Can anticonvulsants be withdrawn in seizure-free persons?
Study design: Practice guideline **Funding source:** Foundation
Synopsis: To update its 1996 recommendations on anticonvulsant withdrawal, the American Academy of Neurology (AAN) convened a panel of clinicians with expertise in epilepsy, a methodologist and general AAN members - no patients or primary care clinicians. The AAN tries to minimize conflicts of interest among the panelists. The panel used systematic reviews to inform their recommendations. The panel addressed various outcomes, generally 12 months or longer after withdrawal: seizure recurrence, quality of life, mortality, and status epilepticus. One of the problems was the variability in seizure-free intervals used in the studies: 12 to 60 months! Ultimately, the panel recommended that for adults who have been seizure-free for 24 months or more, that the patient and clinician engage in shared decision-making as to the benefits and harms of continuing anticonvulsants. The panel could draw no conclusions as to the utility of electroencephalograms or imaging in guiding these decisions among adults. They also could make no recommendations about medication withdrawal after epilepsy surgery. Among children who have abnormal electroencephalograms, the panel does not recommend medication withdrawal. Otherwise, in children who have been seizure-free for 18-24 months, the panel recommends shared decision-making as to the benefits and harms of continuing anticonvulsants. Finally, the panel identified several areas in need of research.
Bottom line: For the most part, the American Academy of Neurology recommends shared decision-making to decide whether to withdraw anticonvulsants among adults and children who have been seizure-free. Now, if they only provided good tools to guide this!
Gloss D, Pargeon K, Pack A, et al. Antiseizure Medication Withdrawal in Seizure-Free Patients: Practice Advisory Update Summary: Report of the AAN Guideline Subcommittee. Neurology. 2021;97(23):1072-1081.

Miscellaneous

15. Anticonvulsants, SNRIs, and rubefacients are best initial choices for chronic pain caused by diabetic neuropathy or postherpetic neuralgia

Clinical question: Which treatments for chronic neuropathic pain can provide clinically meaningful improvement?
Study design: Meta-analysis (randomized controlled trials) **Funding source:** Self-funded or unfunded
Synopsis: This report describes the findings from a series of meta-analyses of placebo-controlled randomized trials of at least 3 months' duration on the effectiveness of drug and nondrug treatments for chronic neuropathic pain, with a focus on diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia. Only studies that provided results as the presence or absence of a clinically meaningful response, defined as at least a 30% improvement on a scale of pain and/or function, were included. Studies in pregnant women, studies of acute pain, and those with an active comparator were excluded. The authors found no qualifying studies for

trigeminal neuralgia, or for topical lidocaine or exercise as interventions. For anticonvulsants, the authors identified 40 randomized controlled trials (RCTs) with moderate certainty of evidence; the bulk of the evidence was for pregabalin and gabapentin and both were effective (number needed to treat [NNT] = 7 for one patient to respond, and a number need to treat to harm [NNTH] of 17 to 22 for withdrawal due to adverse events). Rubefacients (topical drugs that cause irritation and redness of skin) were studied in 10 RCTs with low certainty of evidence; low-dose patches or creams and high-potency patches were similarly effective (NNT = 7) and were generally well tolerated (NNTH = 25 for withdrawal). The SNRIs duloxetine, venlafaxine, and desvenlafaxine were studied in 8 moderate-certainty studies, with an NNT of 7 for response and NNTH of 13 for withdrawal. Opioids were studied in 6 studies of low certainty, with an NNT of 8 for one patient to respond but a similar NNTH of 12 for withdrawal due to adverse events. Acupuncture was only studied in 3 trials with very low certainty; no significant benefit was detected though the confidence interval is wide (relative risk 1.81; 95% CI 0.55 - 6.0). Finally, tricyclic antidepressants were studied in only 2 small low-certainty studies, and no significant benefit was seen in the appropriate random effects meta-analysis. Results are summarized in the table below.

Intervention	Studies (Participants)	NNT	NNTH	Quality
Anticonvulsants	40 (9575)	7	17-22	Moderate
SNRIs	8 (2746)	7	13	Moderate
Rubefacients	10 (2344)	7	25	Low
Opioids	6 (1149)	8	12	Low

Bottom line: Given the balance of benefits and harms, there is moderately good evidence for anticonvulsants (pregabalin and gabapentin were similarly effective and well tolerated) and serotonin-norepinephrine reuptake inhibitors (SNRIs; with duloxetine and venlafaxine being similarly effective and well tolerated). Rubefacients (usually salicylates) appear to be effective but are less well studied with low-quality evidence. Acupuncture, opioids, and tricyclic antidepressants cannot be recommended based on current evidence.
Falk J, Thomas B, Kirkwood J, et al. PEER systematic review of randomized controlled trials: Management of chronic neuropathic pain in primary care. Can Fam Physician 2021;67(5):e130-e140.

16. Midodrine is worth a trial in people with frequent episodes of vasovagal syncope

Clinical question: Can midodrine decrease recurrent episodes of vasovagal syncope?
Study design: Randomized controlled trial (double-blinded) **Funding source:** Industry + govt
Synopsis: These investigators enrolled 133 adults without orthostatic hypotension who had fainted at least twice (median = 6 times) in the past year and who did not have other known causes of syncope, including orthostatic hypotension. Patients were randomized, concealed allocation unknown, to receive either placebo or midodrine for one year. Either treatment was started at 5 mg 3 times daily during daylight hours, with the dose increased up to 10 mg 3 times daily, if tolerated. Over one year, 58% of patients in the midodrine group were syncope-free as compared with 39% in the placebo group (number needed to treat = 5). Midodrine treatment was also associated with a longer time to first recurrence of syncope (P = .035). In the subset of participants who had at least one syncope episode during the study, the rates were similar between treatments (3.6 - 3.8 episodes per year).
Bottom line: Midodrine, a vasoconstrictor used to prevent orthostatic hypotension, may reduce the likelihood of recurrence of vasovagal syncope in patients who have episodes fairly often. It seems to either work completely or not at all; during this study, the patients who had at least one episode of syncope had several episodes over the course of the year regardless of whether they received midodrine or placebo.
Sheldon R, Faris P, Tang A, et al, for the POST 4 investigators. Midodrine for the prevention of vasovagal syncope: a randomized clinical trial. Ann Intern Med 2021;174(10):1349-1356.

17. Anticoagulants for acute ischaemic stroke

Background: Stroke is the third leading cause of early death worldwide. Most ischaemic strokes are caused by a blood clot blocking an artery in the brain. Patient outcomes might be improved if they are offered anticoagulants that reduce their risk of developing new blood clots and do not increase the risk of bleeding. This is an update of a Cochrane Review first published in 1995, with updates in 2004, 2008, and 2015.
Objectives: To assess the effectiveness and safety of early anticoagulation (within the first 14 days of onset) for people with acute presumed or confirmed ischaemic stroke.
Our hypotheses were that, compared with a policy of avoiding their use, early anticoagulation would be associated with:
• reduced risk of death or dependence in activities of daily living a few months after stroke onset;
• reduced risk of early recurrent ischaemic stroke;
• increased risk of symptomatic intracranial and extracranial haemorrhage; and
• reduced risk of deep vein thrombosis and pulmonary embolism.
Search methods: We searched the Cochrane Stroke Group Trials Register (August 2021); the Cochrane Database of Systematic Reviews (CDSR); the Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 7), in the Cochrane Library (searched 5 August 2021); MEDLINE (2014 to 5 August 2021); and Embase (2014 to 5 August 2021). In addition, we searched ongoing trials registries and reference lists of relevant papers. For previous versions of this review, we searched the register of the Antithrombotic Trialists' (ATT) Collaboration, consulted MedStrategy (1995), and contacted relevant drug companies. **Selection criteria:** Randomised trials comparing early anticoagulant therapy (started within two weeks of stroke onset) with control in people with acute presumed or confirmed ischaemic stroke. **Data collection and analysis:** Two review authors independently selected trials for inclusion, assessed trial quality, and extracted data. We assessed the overall certainty of the evidence for each outcome using RoB1 and GRADE methods.
Main results: We included 28 trials involving 24,025 participants. Quality of the trials varied considerably. We considered some studies to be at unclear or high risk of selection, performance, detection, attrition, or reporting bias. Anticoagulants tested were standard

unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. Over 90% of the evidence is related to effects of anticoagulant therapy initiated within the first 48 hours of onset. No evidence suggests that early anticoagulation reduced the odds of death or dependence at the end of follow-up (odds ratio (OR) 0.98, 95% confidence interval (CI) 0.92 to 1.03; 12 RCTs, 22,428 participants; high-certainty evidence). Similarly, we found no evidence suggesting that anticoagulant therapy started within the first 14 days of stroke onset reduced the odds of death from all causes (OR 0.99, 95% CI 0.90 to 1.09; 22 RCTs, 22,602 participants; low-certainty evidence) during the treatment period. Although early anticoagulant therapy was associated with fewer recurrent ischaemic strokes (OR 0.75, 95% CI 0.65 to 0.88; 12 RCTs, 21,665 participants; moderate-certainty evidence), it was also associated with an increase in symptomatic intracranial haemorrhage (OR 2.47; 95% CI 1.90 to 3.21; 20 RCTs, 23,221 participants; moderate-certainty evidence). Similarly, early anticoagulation reduced the frequency of symptomatic pulmonary emboli (OR 0.60, 95% CI 0.44 to 0.81; 14 RCTs, 22,544 participants; high-certainty evidence), but this benefit was offset by an increase in extracranial haemorrhage (OR 2.99, 95% CI 2.24 to 3.99; 18 RCTs, 22,255 participants; moderate-certainty evidence).
Authors' conclusions: Since the last version of this review, four new relevant studies have been published, and conclusions remain consistent. People who have early anticoagulant therapy after acute ischaemic stroke do not demonstrate any net short- or long-term benefit. Treatment with anticoagulants reduced recurrent stroke, deep vein thrombosis, and pulmonary embolism but increased bleeding risk. Data do not support the routine use of any of the currently available anticoagulants for acute ischaemic stroke.
Wang X, Ouyang M, Yang J, Song L, Yang M, Anderson CS. Anticoagulants for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2021, Issue 10. Art. No.: CD000024. DOI: 10.1002/14651858.CD000024.pub5.

18. Antiplatelet therapy vs no antiplatelet therapy after intracranial hemorrhage: similar rates of subsequent bleeds and major vascular events (RESTART)

Clinical Question
What are the benefits and harms of continued antiplatelet therapy in persons who have had an intracranial hemorrhage?
Study Design: Randomized controlled trial (single-blinded)
Synopsis: This study included adults who survived at least 24 hours after an intracranial hemorrhage (ICH) and who had their antithrombic therapy discontinued. The patients were randomized to antiplatelet therapy (aspirin, dipyridamole, or clopidogrel as monotherapy or dual therapy; n = 268) or antiplatelet avoidance (n = 268). Although the allocation was concealed, only the research staff conducting follow-up and those assessing outcome events were masked to group assignment. The study was set up so that all survivors had at least 2 years of follow-up. After a median 7 years of follow-up, the rate of subsequent ICH was similar for those receiving antiplatelet therapy as for those who were not (9.3% vs 8.2%). Additionally, the authors found no statistically significant difference in the rate of major vascular events (26.8% vs 32.5%). Since the study was designed to recruit 720 patients, this report may lack the power to detect these differences. This is less of a concern since the rate of subsequent ICH was lower for those treated with antiplatelet agents (a counterintuitive result); but for a high-risk group, the rate of major vascular events is potentially important (number needed to treat = 18). Finally, these data are comparable with findings from observational studies.
Bottom Line
In this slightly underpowered study, starting antiplatelet therapy after an ICH does not appear to be more harmful than avoiding antiplatelet therapies.
Al-Shahi Salman R, Dennis MS, Sandercock PAG, et al, for the RESTART Collaboration. Effects of antiplatelet therapy after stroke caused by intracerebral hemorrhage: extended follow-up of the RESTART randomized clinical trial. JAMA Neurol 2021;78(10):1179-1186.

19. Fewer strokes but more bleeding with aspirin + either clopidogrel or ticagrelor than with monotherapy in secondary stroke prevention

Clinical question: Is dual therapy with ticagrelor and aspirin more effective than monotherapy or dual therapy with aspirin and other antiplatelet agents in the secondary prevention of strokes?
Study design: Meta-analysis (randomized controlled trials) **Funding source:** Government
Synopsis: These investigators were interested in determining the relative effectiveness of dual therapy with aspirin plus ticagrelor versus dual therapy with aspirin plus clopidogrel, dual therapy with aspirin plus prasugrel, or monotherapy. To do this, they searched MEDLINE, EMBASE, and the Cochrane Library to identify randomized trials that reported 30-day stroke outcomes of P2Y12 antiplatelet agent (ticagrelor, clopidogrel, or prasugrel) or aspirin monotherapies and combination therapies in adults with cerebrovascular, coronary, or peripheral artery disease. To be included, the studies had to include ticagrelor. The authors pooled all the data to conduct a network meta-analysis, which allows for multiple comparisons in the absence of head-to-head studies. Once the authors selected articles for inclusion, they applied the Cochrane risk of bias tool. Ultimately, they included 26 trials with 124,495 participants. The dosages for the various agents varied: ticagrelor 60 or 90 mg twice daily; clopidogrel 75 mg once daily, prasugrel 10 mg once daily and aspirin 75 to 150 mg daily. Overall, the included studies were at low risk of bias. Compared with aspirin alone, the combination of aspirin and clopidogrel was the most effective at preventing stroke (relative risk [RR] 0.77; 95% CI 0.62 - 0.96) followed by aspirin plus ticagrelor (RR 0.80; 0.72 - 0.89). Neither aspirin plus prasugrel, monotherapy with clopidogrel, nor monotherapy with ticagrelor statistically significantly reduced strokes. Additionally, compared with aspirin alone, combination therapy with clopidogrel, ticagrelor, and prasugrel each had twice the risk of major bleeding, while monotherapy with clopidogrel or ticagrelor were comparable with aspirin. The authors found little heterogeneity among these data. None of the regimens significantly decreased all-cause mortality. Finally, the reporting of the data prevents estimating the numbers needed to treat for benefit or for harm.
Bottom line: Although the authors focus on the combination of aspirin and ticagrelor, aspirin plus clopidogrel was actually slightly more effective than aspirin plus ticagrelor or monotherapy with aspirin or other P2Y12 antiplatelet agents in preventing strokes. Dual antiplatelet therapy with any P2Y12 agent plus aspirin, however, causes more major bleeding. Finally, this study was not intended to be a comprehensive analysis of *all* antiplatelet medications.
Balint A, Tornyos D, El Alaoui El Abdallaoui O, Kupo P, Komocsi A. Network meta-analysis of ticagrelor for stroke prevention in patients at high risk for cardiovascular or cerebrovascular events. Stroke 2021;52(9):2809-2816.

Bottom Lines:

- Regardless of age or the presence of underlying medical or psychiatric conditions, nonpharmacologic approaches are the preferred approach to managing sleep disorders
- Clinical features can be used to accurately identify which children do not need imaging following head injury.
- After concussion, graded symptom-limited activities can facilitate return to activity.
- The primary approach to managing febrile seizures is in reassurance, education and fever control and to minimize the use of anticonvulsants.
- Seizure-free adults and children are candidates for withdrawing anticonvulsants, however, this requires shared decision-making about the potential benefits and harms.
- Anticoagulation after acute ischemic stroke prevents recurrent stroke and VTE, but increases the risk of symptomatic intracranial hemorrhage and major extracranial bleeding
- The rate of events after resuming antiplatelet therapy after intracranial hemorrhage is similar to the event rate in those not resuming it – this is a place of shared decision-making
- Dual antiplatelet therapy for secondary stroke prevention in high-risk adults is more effective than monotherapy but doubles to risk of bleeding.

Lipid Update — Gary Ferenchick MD

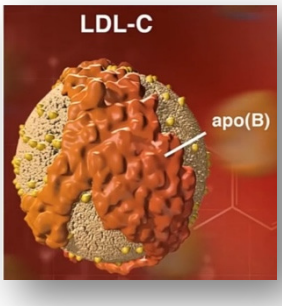
Learning objectives | Understand and apply:

- The uses of ApoB and Lp(a) as ancillary markers of ASCVD risk
- Use of coronary artery calcium (CAC) scoring in adjusting risk in patients at an intermediate 10-year risk of ASCVD
- Studies on statin safety & intolerance

Lipoproteins and Apolipoproteins

Oil and water don't mix. Blood lipids can only be transported with a protein "shell". This combo of a core of lipid with a protein shell is called a *lipoprotein*. 6 major lipoproteins exist in the blood: There are 6 non-HDL lipoproteins: 1) chylomicrons, 2) chylomicron remnants 3) very low density lipoprotein (VLDL),4) intermediate density lipoprotein (IDL), 5) low density lipoprotein LDL; 6) lipoprotein(a) or Lp(a); and 1 HDL lipoprotein. The protein shell of these lipoproteins are called *apolipoproteins*, there are 2 major apolipoproteins. **apo B** encapsulate all non-HDL cholesterol; **apo A1** encapsulates HDL

A paradigm is being forwarded that atherogenic hyperlipidemia is more than just LDL.



apo B is emerging as a strong marker of coronary heart disease risk. apoB is the protein that is contained in all "bad cholesterol" not just LDL. This "bad cholesterol" is also called non-HDL cholesterol.

Importantly apoB can be thought of as a marker of residual risk in those with at target LDL levels. Meaning substantial residual risk remains even among groups treated to appropriate LDL target.

Problems with only using LDL as a marker of CVD risk include: 1) The LDL cholesterol that you order on a regular basis as part of your lipid panel is not *direc*tly measured, but is calculated using the Friedewald equation: LDL = Total cholesterol minus HDL cholesterol minus triglycerides/5, and many assumptions are "built in" to this equation, and 2) The cholesterol *content of LDL particles varies*.
The potential benefits of measuring apoB include: 1) apoB is measured directly (i.e., not calculated) and 2) Each apoB containing lipoprotein particle always has a single apoB molecule; therefore, *apoB equals atherogenic particle number*. On average, people with higher concentrations of plasma apoB-containing lipoproteins will retain more particles in the arterial wall, and accumulate lipids faster, resulting in more rapid growth and the progression of atherosclerotic plaques.

As alluded to, (and adding to confusion – at least mine!), lipoprotein(a) {Lp(a)} is a modified form of LDL that has atherogenic (and thrombogenic) potential. Lp(a) contains ApoB & apolipoprotein(a). Remember this is not to be confused with ApoA1 which is the protein shell of HDL. (Confused yet?)

In the observational following study," …LDL-C and non-HDL-C become nonsignificant markers of risk when apoB is taken into account"

Coronary Artery Disease | Risk

1. MI risk assessment > with apoB assessment than with LDL Cholesterol

Importance: Lipid management typically focuses on levels of low-density lipoprotein cholesterol (LDL-C) and, to a lesser extent, triglycerides (TG). However, animal models and genetic studies suggest that the atherogenic particle subpopulations (LDL and very-low-density lipoprotein [VLDL]) are both important and that the number of particles is more predictive of cardiac events than their lipid content.

Objective: To determine whether common measures of cholesterol concentration, TG concentration, or their ratio are associated with cardiovascular risk beyond the number of apolipoprotein B (apoB)–containing lipoproteins.
Design, Setting, and Participants: This prospective cohort analysis included individuals from the population-based UK Biobank and from 2 large international clinical trials, FOURIER and IMPROVE-IT. The median (IQR) follow-up was 11.1 (10.4-11.8) years in UK Biobank and 2.5 (2.0-4.7) years in the clinical trials. Two populations were studied in this analysis: 389 529 individuals in the primary prevention group who were not taking lipid-lowering therapy and 40 430 patients with established atherosclerosis who were receiving statin treatment.
Exposures: ApoB, non–high-density lipoprotein cholesterol (HDL-C), LDL-C, and TG.
Main Outcome and Measures: The primary study outcome was incident myocardial infarction (MI).
Results: Of the 389 529 individuals in the primary prevention group, 224 097 (58%) were female, and the median (IQR) age was 56.0 (49.5-62.5) years. Of the 40 430 patients with established atherosclerosis, 9647 (24%) were female, and the median (IQR) age was 63 (56.2-69.0) years. In the primary prevention cohort, apoB, non–HDL-C, and TG each individually were associated with incident MI. However, when assessed together, only apoB was associated (adjusted hazard ratio [aHR] per 1 SD, 1.27; 95% CI, 1.15-1.40; P < .001). Similarly, only apoB was associated with MI in the secondary prevention cohort. Adjusting for apoB, there was no association between the ratio of TG to LDL-C (a surrogate for the ratio of TG-rich lipoproteins to LDL) and risk of MI, implying that for a given concentration of apoB-containing lipoproteins, the relative proportions of particle subpopulations may no longer be a predictor of risk.
Conclusions and Relevance: In this cohort study, risk of MI was best captured by the number of apoB-containing lipoproteins, independent from lipid content (cholesterol or TG) or type of lipoprotein (LDL or TG-rich). This suggests that apoB may be the primary driver of atherosclerosis and that lowering the concentration of all apoB-containing lipoproteins should be the focus of therapeutic strategies.
Reference: Association of Apolipoprotein B–Containing Lipoproteins and Risk of Myocardial Infarction in Individuals With and Without Atherosclerosis Distinguishing Between Particle Concentration, Type, and Content. JAMA Cardiol. Published online November 13, 2021. doi:10.1001/jamacardio.2021.5083

Residual risk of CVD in statin treated patients is better estimated with ↑ apoB and ↑ non-HDL cholesterol than ↑ LDL-C

2. ApoB better estimates residual risk in statin treated patients

Background: In cholesterol guidelines, low-density lipoprotein (LDL) cholesterol remains the primary target while apolipoprotein B (apoB) and non–high-density lipoprotein (non-HDL) cholesterol are secondary targets.
Objectives: This study sought to determine if elevated apoB and/or non-HDL cholesterol are superior to elevated LDL cholesterol in identifying statin-treated patients at residual risk of all-cause mortality and myocardial infarction.
Methods: In total, 13,015 statin-treated patients from the Copenhagen General Population Study were included with 8 years median follow-up. Cox regressions among apoB, non-HDL cholesterol, and LDL cholesterol, respectively, and all-cause mortality or myocardial infarction were examined on continuous scales by restricted cubic splines and by categories of concordant and discordant values defined by medians.
Results: High apoB and non-HDL cholesterol were associated with increased risk of all-cause mortality and myocardial infarction, whereas no such associations were found for high LDL cholesterol. Compared with concordant values below medians, discordant apoB above the median with LDL cholesterol below yielded hazard ratios of 1.21 (95% confidence interval [CI]: 1.07 to 1.36) for all-cause mortality and 1.49 (95% CI: 1.15 to 1.92) for myocardial infarction. Corresponding values for high non-HDL cholesterol with low LDL cholesterol were 1.18 (95% CI: 1.02 to 1.36) and 1.78 (95% CI: 1.35 to 2.34). In contrast, discordant high LDL cholesterol with low apoB or non-HDL cholesterol was not associated with increased risk of all-cause mortality or myocardial infarction. Also, discordant high apoB with low non-HDL cholesterol yielded hazard ratios of 1.21 (95% CI: 1.03 to 1.41) for all-cause mortality and of 0.93 (95% CI: 0.62 to 1.40) for myocardial infarction. Furthermore, dual discordant apoB and non-HDL cholesterol above the medians with LDL cholesterol below presented hazard ratios of 1.23 (95% CI: 1.07 to 1.43) for all-cause mortality and 1.82 (95% CI: 1.37 to 2.42) for myocardial infarction.
Conclusions: In statin-treated patients, elevated apoB and non-HDL cholesterol, but not LDL cholesterol, are associated with residual risk of all-cause mortality and myocardial infarction. Discordance analysis demonstrates that apoB is a more accurate marker of all-cause mortality risk in statin-treated patients than LDL cholesterol or non-HDL cholesterol, and apoB in addition is a more accurate marker of risk of myocardial infarction than LDL cholesterol.
Reference: Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. J AmColl Cardiol. 2021;77(11):1439-1450.

However not all observational studies have identified added benefit from measuring ApoB

3. ApoB no better predictor than total cholesterol and HDL-C

Background: Total cholesterol and high-density lipoprotein cholesterol (HDL-C) measurements are central to cardiovascular disease (CVD) risk assessment, but there is continuing debate around the utility of other lipids for risk prediction.
Methods: Participants from UK Biobank without baseline CVD and not taking statins, with relevant lipid measurements (n=346 686), were included in the primary analysis. An incident fatal or nonfatal CVD event occurred in 6216 participants (1656 fatal) over a median of 8.9 years. Associations of nonfasting lipid measurements (total cholesterol, HDL-C, non-HDL-C, direct and calculated low-density lipoprotein cholesterol [LDL-C], and apolipoproteins [Apo] A1 and B) with CVD were compared using Cox models adjusting for classical risk factors, and predictive utility was determined by the C-index and net reclassification index. Prediction was also tested in 68 649 participants taking a statin with or without baseline CVD (3515 CVD events).

Results: ApoB, LDL-C, and non-HDL-C were highly correlated (r>0.90), while HDL-C was strongly correlated with ApoA1 (r=0.92). After adjustment for classical risk factors, 1 SD increase in ApoB, direct LDL-C, and non-HDL-C had similar associations with composite fatal/nonfatal CVD events (hazard ratio, 1.23, 1.20, 1.21, respectively). Associations for 1 SD increase in HDL-C and ApoA1 were also similar (hazard ratios, 0.81 [both]). Adding either total cholesterol and HDL-C, or ApoB and ApoA, to a CVD risk prediction model (C-index, 0.7378) yielded similar improvement in discrimination (C-index change, 0.0084; 95% CI, 0.0065, 0.0104, and 0.0089; 95% CI, 0.0069, 0.0109, respectively). Once total and HDL-C were in the model, no further substantive improvement was achieved with the addition of ApoB (C-index change, 0.0004; 95% CI, 0.0000, 0.0008) or any measure of LDL-C. Results for predictive utility were similar for a fatal CVD outcome, and in a discordance analysis. In participants taking a statin, classical risk factors (C-index, 0.7118) were improved by non-HDL-C (C-index change, 0.0030; 95% CI, 0.0012, 0.0048) or ApoB (C-index change, 0.0030; 95% CI, 0.0011, 0.0048). However, adding ApoB or LDL-C to a model already containing non-HDL-C did not further improve discrimination.
Conclusions: Measurement of total cholesterol and HDL-C in the nonfasted state is sufficient to capture the lipid-associated risk in CVD prediction, with no meaningful improvement from addition of apolipoproteins, direct or calculated LDL-C.
Reference: Comparison of Conventional Lipoprotein Tests and Apolipoproteins in the Prediction of Cardiovascular Disease. Circulation. 2019 Aug 13;140(7):542-552

According to Sniderman (a strong advocate of using ApoB) (JAMA Cardiol 2022;7:257)

- "Trapping of apoB particles is the fundamental cause of atherosclerosis and the number of apoB particles in plasma is the most important driver of this trapping within the arterial wall."
- "Apo B "far less prone to measurement error than LDL-C (which is a calculated number) or non-HDL-C"
- "To assess the adequacy of therapy for the atherogenic dyslipoproteinemias … apoB is all that needs to be measured, a change that would simplify and improve care."
- "Rather than discussing "bad cholesterol," we shift to discussing the "number of bad cholesterol particles"

What do the guidelines say?

European Guidelines

Regarding apoB, in 2019 the European Society of Cardiology and the European Atherosclerosis Society published "Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk" (European Heart Journal (2020) 41, 111-188). Among their recommendations included:

- "… that lowering LDL particles and other ApoB-containing lipoproteins as much as possible reduces CV events."
- "ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C."
- "It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C."

American Guidelines

- The ACC AHA 2018 guideline states that an indication for measuring apoB is in a person with triglycerides ≥200 mg/dL. In this context, an apoB level ≥130 mg/dL corresponds to an LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor. (Circulation 2019;139:e1082)

Lipoprotein(a) {Lp(a)}

- Lp(a) is a modified form of LDL with atherogenic potential.
- Lp(a) is an apoB-containing lipoprotein and has a "tail of Apo(a)
- Epidemiological, genome-wide association, and Mendelian randomization data provide clear support for a causal role for elevated Lp(a) in the development of atherosclerotic cardiovascular disease (ASCVD). (Arterioscler Thromb Vasc Biol. 2022;42:e48–e60)
- 70 – 90% of Lp(a) is genetically determined

4. Lowering Lp(a) is possible, clinical outcomes uncertain

BACKGROUND: Lipoprotein(a) levels are genetically determined and, when elevated, are a risk factor for cardiovascular disease and aortic stenosis. There are no approved pharmacologic therapies to lower lipoprotein(a) levels.
METHODS: We conducted a randomized, double-blind, placebo-controlled, dose-ranging trial involving 286 patients with established cardiovascular disease and screening lipoprotein(a) levels of at least 60 mg per deciliter (150 nmol per liter). Patients received the hepatocyte-directed antisense oligonucleotide AKCEA-APO(a)-LRx, referred to here as APO(a)-LRx (20, 40, or 60 mg every 4 weeks; 20 mg every 2 weeks; or 20 mg every week), or saline placebo subcutaneously for 6 to 12 months. The lipoprotein(a) level was measured with an isoform-independent assay. The primary end point was the percent change in lipoprotein(a) level from baseline to month 6 of exposure (week 25 in the groups that received monthly doses and week 27 in the groups that received more frequent doses).
RESULTS: The median baseline lipoprotein(a) levels in the six groups ranged from 204.5 to 246.6 nmol per liter. Administration of APO(a)-LRx resulted in dose-dependent decreases in lipoprotein(a) levels, with mean percent decreases of 35% at a dose of 20 mg every 4 weeks, 56% at 40 mg every 4 weeks, 58% at 20 mg every 2 weeks, 72% at 60 mg every 4 weeks, and 80% at 20 mg every week, as compared with 6% with placebo (P values for the comparison with placebo ranged from 0.003 to <0.001). There were no significant differences between any APO(a)-LRx dose and placebo with respect to platelet counts, liver and renal measures, or influenza-like symptoms. The most common adverse events were injection-site reactions.
CONCLUSIONS: APO(a)-LRx reduced lipoprotein(a) levels in a dose-dependent manner in patients who had elevated lipoprotein(a) levels and established cardiovascular disease.
REFERENCE: Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. N Engl J Med 2020; 382:244-255

According to the ACC,

- "…if a decision is made to measure Lp(a), an Lp(a) ≥50 mg/dL or ≥125 nmol/L, Lp(a) may be considered a risk-enhancing factor"

Can Coronary Artery Calcium Scores (CACs) modify estimated ASCVD risk

The ACC AHA endorses the use of CAC scores in patients with whom starting a statin remains uncertain (e.g., in patients with intermediate CV risk (i.e. 7.5 to 19.9%) and who would like more definitive and specific evidence of need for potentially life long therapy. CAC scores have the potential to "de-risk" certain patients. Previous studies have shown that the risk of ASCVD in those with CAC scores of zero fall below the threshold for starting a stain (< 6% 10-year risk of ASCVD).

For example, the following table shows that in those with calculated 10-year risks of ~ 14%, the "actual" event rates in those with a CAC score of zero was 3.2%

All patients (n = 6,814) had a means calculated 10-year Framingham risk of an ASCVD event of ~ 14% | 11.1 years of follow up		
N	**CAC Score**	**ASCVD Events (%)**
3400	0	3.2%
1787	0-100	7.9%
755	100-300	13.3%
841	>300	17.4%
ASCVD event = stroke, cardiovascular death or non-fatal MI		
Budoff MJ et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). Eur Heart J. 2018 Jul 1;39(25):2401-2408		

The following study incorporated Lp(a) and ApoB risk enhancing factor measurement – and essentially found that, much like above, a CAC of zero in those with elevated levels still was associated with low ASCVD risk

5. CAC scores of zero associated with low ASCVD event rates even in those with multiple risk enhancing factors

Importance: The 2018 American Heart Association/American College of Cardiology Guideline on the Management of Blood Cholesterol recommends the use of risk-enhancing factor assessment and the selective use of coronary artery calcium (CAC) scoring to guide the allocation of statin therapy among individuals with an intermediate risk of atherosclerotic cardiovascular disease (ASCVD).
Objective: To examine the association between risk-enhancing factors and incident ASCVD by CAC burden among those at intermediate risk of ASCVD.
Design, setting, and participants: The Multi-Ethnic Study of Atherosclerosis is a multicenter population-based prospective cross-sectional study conducted in the US. Baseline data for the present study were collected between July 15, 2000, and July 14, 2002, and follow-up for incident ASCVD events was ascertained through August 20, 2015. Participants were aged 45 to 75 years with no clinical ASCVD or diabetes at baseline, were at intermediate risk of ASCVD (≥7.5% to <20.0%), and had a low-density lipoprotein cholesterol level of 70 to 189 mg/dL.
Exposures: Family history of premature ASCVD, premature menopause, metabolic syndrome, chronic kidney disease, lipid and inflammatory biomarkers, and low ankle-brachial index.
Main outcomes and measures: Incident ASCVD over a median follow-up of 12.0 years.
Results: A total of 1688 participants (mean [SD] age, 65 [6] years; 976 men [57.8%]). Of those, 648 individuals (38.4%) were White, 562 (33.3%) were Black, 305 (18.1%) were Hispanic, and 173 (10.2%) were Chinese American. A total of 722 participants (42.8%) had a CAC score of 0. Among those with 1 to 2 risk-enhancing factors vs those with 3 or more risk-enhancing factors, the prevalence of a CAC score of 0 was 45.7% vs 40.3%, respectively. Over a median follow-up of 12.0 years (interquartile range [IQR], 11.5-12.6 years), the unadjusted incidence rate of ASCVD among those with a CAC score of 0 was less than 7.5 events per 1000 person-years for all individual risk-enhancing factors (with the exception of ankle-brachial index, for which the incidence rate was 10.4 events per 1000 person-years [95% CI, 1.5-73.5]) and combinations of risk-enhancing factors, including participants with 3 or more risk-enhancing factors. Although the individual and composite addition of risk-enhancing factors to the traditional risk factors was associated with improvement in the area under the receiver operating curve, the use of CAC scoring was associated with the greatest improvement in the C statistic (0.633 vs 0.678) for ASCVD events. For incident ASCVD, the net reclassification improvement for CAC was 0.067.
Conclusions and relevance: In this cross-sectional study, among participants with CAC scores of 0, the presence of risk-enhancing factors was generally not associated with an overall ASCVD risk that was higher than the recommended treatment threshold for the initiation of statin therapy. The use of CAC scoring was associated with significant improvements in the reclassification and discrimination of incident ASCVD. The results of this study support the utility of CAC scoring as an adjunct to risk-enhancing factor assessment to more accurately classify individuals with an intermediate risk of ASCVD who might benefit from statin therapy.
Reference: Assessment of Coronary Artery Calcium Scoring to Guide Statin Therapy Allocation According to Risk-Enhancing Factors: The Multi-Ethnic Study of Atherosclerosis. JAMA Cardiol 2021 Oct 1;6(10):1161-1170.
In patients at intermediate risk for ASCVD, a CAC score of zero suggests a risk level below the recommended threshold for treatment.

Statins & ADEs

6. ADE from Statin Use = Low

Objective: To assess the associations between statins and adverse events in primary prevention of cardiovascular disease and to examine how the associations vary by type and dosage of statins.
Design: Systematic review and meta-analysis.
Data sources: Studies were identified from previous systematic reviews and searched in Medline, Embase, and the Cochrane Central Register of Controlled Trials, up to August 2020.
Review methods: Randomised controlled trials in adults without a history of cardiovascular disease that compared statins with non-statin controls or compared different types or dosages of statins were included.
Main outcome measures: Primary outcomes were common adverse events: self-reported muscle symptoms, clinically confirmed muscle disorders, liver dysfunction, renal insufficiency, diabetes, and eye conditions. Secondary outcomes included myocardial infarction, stroke, and death from cardiovascular disease as measures of efficacy.
Data synthesis: A pairwise meta-analysis was conducted to calculate odds ratios and 95% confidence intervals for each outcome between statins and non-statin controls, and the absolute risk difference in the number of events per 10 000 patients treated for a year was estimated. A network meta-analysis was performed to compare the adverse effects of different types of statins. An Emax model based meta-analysis was used to examine the dose-response relationships of the adverse effects of each statin.
Results: 62 trials were included, with 120 456 participants followed up for an average of 3.9 years. Statins were associated with an increased risk of self-reported muscle symptoms (21 trials, odds ratio 1.06 (95% confidence interval 1.01 to 1.13); absolute risk difference 15 (95% confidence interval 1 to 29)), liver dysfunction (21 trials, odds ratio 1.33 (1.12 to 1.58); absolute risk difference 8 (3 to 14)), renal insufficiency (eight trials, odds ratio 1.14 (1.01 to 1.28); absolute risk difference 12 (1 to 24)), and eye conditions (six trials, odds ratio 1.23 (1.04 to 1.47); absolute risk difference 14 (2 to 29)) but were not associated with clinically confirmed muscle disorders or diabetes. The increased risks did not outweigh the reduction in the risk of major cardiovascular events. Atorvastatin, lovastatin, and rosuvastatin were individually associated with some adverse events, but few significant differences were found between types of statins. An Emax dose-response relationship was identified for the effect of atorvastatin on liver dysfunction, but the dose-response relationships for the other statins and adverse effects were inconclusive.
Conclusions: For primary prevention of cardiovascular disease, the risk of adverse events attributable to statins was low and did not outweigh their efficacy in preventing cardiovascular disease, suggesting that the benefit-to-harm balance of statins is generally favourable. Evidence to support tailoring the type or dosage of statins to account for safety concerns before starting treatment was limited.
Reference: Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. BMJ 2021 Jul 14;374:n1537. doi: 10.1136/bmj.n1537.

7. Sx Caused by Statins = Nocebo

Background: Most people who begin statins abandon them, most commonly because of side effects.
Objectives: The purpose of this study was to assess daily symptom scores on statin, placebo, and no treatment in participants who had abandoned statins.
Methods: Participants received 12 1-month medication bottles, 4 containing atorvastatin 20 mg, 4 placebo, and 4 empty. We measured daily symptom intensity for each using an app (scale 1-100). We also measured the "nocebo" ratio: the ratio of symptoms induced by taking statin that was also induced by taking placebo.
Results: A total of 60 participants were randomized and 49 completed the 12-month protocol. Mean symptom score was 8.0 (95% CI: 4.7-11.3) in no-tablet months. It was higher in statin months (16.3; 95% CI: 13.0-19.6; P < 0.001), but also in placebo months (15.4; 95% CI: 12.1-18.7; P < 0.001), with no difference between the 2 (P = 0.388). The corresponding nocebo ratio was 0.90. In the individual-patient daily data, neither symptom intensity on starting (OR: 1.02; 95% CI: 0.98-1.06; P = 0.28) nor extent of symptom relief on stopping (OR: 1.01; 95% CI: 0.98-1.05; P = 0.48) distinguished between statin and placebo. Stopping was no more frequent for statin than placebo (P = 0.173), and subsequent symptom relief was similar between statin and placebo. At 6 months after the trial, 30 of 60 (50%) participants were back taking statins.
Conclusions: The majority of symptoms caused by statin tablets were nocebo. Clinicians should not interpret symptom intensity or timing of symptom onset or offset (on starting or stopping statin tablets) as indicating pharmacological causation, because the pattern is identical for placebo. .
Reference: Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment. J Am Coll Cardiol. 2021 Sep, 78 (12) 1210–1222

N-of-1 Trials

In a trial of 60 patients who previously discontinued statins because of side effects and were enrolled in a double-blind, three-group, n-of-1 trial to test whether symptoms would be induced by a statin or placebo, 90% of the symptoms elicited by a statin challenge was also elicited by placebo."
Reference: N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects. N Engl J Med 2020; 383:2182-2184

8. Unblinded N-of-1 trial increases uptake of statins

Background: The aim was to assess whether an intervention incorporating a practicable open-label n-of-1 trial would lead to greater uptake of statin than usual care and comparable uptake to a closed-label gold-standard n-of-1 trial.
Methods: We enrolled patients who had stopped or declined statins into a 3-arm trial (usual care, unblinded, and blinded n-of-1 intervention arms). Physicians advised participants randomized to usual care to take statin therapy to prevent cardiovascular disease. In both intervention arms, physicians delivered a theoretically informed informed intervention endorsing the value of experimenting with medication in n-of-1 trials to assess whether it caused side-effects. In these trials, participants alternated between 4 weeks of medication and no medication (unblinded arm) or randomly sorted active and placebo (blinded arm) and recorded symptoms and symptom attributions for 6 months. Thereafter, physicians discussed participants' symptom reports during active/inactive treatment periods and asked participants to resume statins if appropriate.
Results: Seventy-three were randomized to the intervention arms and 20 to the control group. Fifty-six of 73 (77%) attempted the n-of-1 experiment; 28/36 (78%) in the unblinded arm; and 28/37 (76%) in the blinded arm. Forty-three of 56 (77%) completed the 6-month experiment and received feedback from the physician; 20/28 (71%) in the unblinded arm and 23/28 (82%) in the blinded arm. Thirty-three of 76 (45%) people restarted statins in the n-of-1 arms compared with 4/20 (20%) in the control arm, difference 24% (95% CI, 5%–43%; P=0.041). There was no evidence this differed between blinded and unblinded arms, difference 2% (95% CI, −20% to 24%; P=0.86). Adverse events occurred at a similar rate on and off statin.
Conclusions: In patients refusing or intolerant of statin, supporting experimentation with n-of-1 trials increases medication uptake compared with usual care. Alternating on-off medication in unblinded n-of-1 experiments appears as effective as a blinded experiment.
Reference: Unblinded and Blinded N-of-1 Trials Versus Usual Care: A Randomized Controlled Trial to Increase Statin Uptake in Primary Care. Circulation: Cardiovascular Quality and Outcomes. 2022;0:10.1161/CIRCOUTCOMES.120.007793

9. Risk of muscle sx assoc with statins = placebo

Objective: To establish the effect of statins on muscle symptoms in people who had previously reported muscle symptoms when taking statins.
Design: Series of randomised, placebo controlled n-of-1 trials.
Setting: Primary care across 50 sites in the United Kingdom, December 2016 to April 2018.
Participants: 200 participants who had recently stopped or were considering stopping treatment with statins because of muscle symptoms.
Interventions: Participants were randomised to a sequence of six double blinded treatment periods (two months each) of atorvastatin 20 mg daily or placebo.
Main outcome measures: At the end of each treatment period, participants rated their muscle symptoms on a visual analogue scale (0-10). The primary analysis compared symptom scores in the statin and placebo periods.
Results: 151 participants provided symptoms scores for at least one statin period and one placebo period and were included in the primary analysis. Overall, no difference in muscle symptom scores was found between the statin and placebo periods (mean difference statin minus placebo -0.11, 95% confidence interval -0.36 to 0.14; P=0.40)). Withdrawals because of intolerable muscle symptoms were 18 participants (9%) during a statin period and 13 (7%) during a placebo period. Two thirds of those completing the trial reported restarting long term treatment with statins.

Conclusions: No overall effect of atorvastatin 20 mg on muscle symptoms compared with placebo was found in participants who had previously reported severe muscle symptoms when taking statins. Most people completing the trial intended to restart treatment with statins. N-of-1 trials can assess drug effects at the group level and guide individual treatment.
Reference: Statin treatment and muscle symptoms: series of randomised, placebo-controlled n-of-1 trials. BMJ 2021;372:n135.

10. Statin Safety | AHA Scientific Statement

One in 4 Americans >40 years of age takes a statin to reduce the risk of myocardial infarction, ischemic stroke, and other complications of atherosclerotic disease. The most effective statins produce a mean reduction in low-density lipoprotein cholesterol of 55% to 60% at the maximum dosage, and 6 of the 7 marketed statins are available in generic form, which makes them affordable for most patients. Primarily using data from randomized controlled trials, supplemented with observational data where necessary, this scientific statement provides a comprehensive review of statin safety and tolerability. The review covers the general patient population, as well as demographic subgroups, including the elderly, children, pregnant women, East Asians, and patients with specific conditions such as chronic disease of the kidney and liver, human immunodeficiency viral infection, and organ transplants. The risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%, and the risk of serious hepatotoxicity is ≈0.001%. The risk of statin-induced newly diagnosed diabetes mellitus is ≈0.2% per year of treatment, depending on the underlying risk of diabetes mellitus in the population studied. In patients with cerebrovascular disease, statins possibly increase the risk of hemorrhagic stroke; however, they clearly produce a greater reduction in the risk of atherothrombotic stroke and thus total stroke, as well as other cardiovascular events. There is no convincing evidence for a causal relationship between statins and cancer, cataracts, cognitive dysfunction, peripheral neuropathy, erectile dysfunction, or tendonitis. In US clinical practices, roughly 10% of patients stop taking a statin because of subjective complaints, most commonly muscle symptoms without raised creatine kinase. In contrast, in randomized clinical trials, the difference in the incidence of muscle symptoms without significantly raised creatine kinase in statin-treated compared with placebo-treated participants is <1%, and it is even smaller (0.1%) for patients who discontinued treatment because of such muscle symptoms. This suggests that muscle symptoms are usually not caused by pharmacological effects of the statin. Restarting statin therapy in these patients can be challenging, but it is important, especially in patients at high risk of cardiovascular events, for whom prevention of these events is a priority. Overall, in patients for whom statin treatment is recommended by current guidelines, the benefits greatly outweigh the risks.
Reference: Medication Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2019 Feb;39(2):e38-e81

11. National Lipid Assoc Statement on Statin Intolerance

- Statin intolerance is reported in 5% - 30% of patients
- Retrial to confirm sx after a washout period
- For patients with suspected statin intolerance, clinicians should attempt multiple strategies to identify a tolerable statin regimen (e.g., lower dose, switching statins, non-daily dosing), because complete statin intolerance is uncommon (<5% of patients).

Modifiable factors associated with statin intolerance
Hypothyroidism
Other meds (protease inhibitors, amiodarone, calcium channel blockers, some antifungals)
Alcohol use
Strenuous exercise
Vitamin D Deficiency
Obesity
DM

- For patients with statin intolerance, it is reasonable to consider the nocebo effect as a possible cause; however, this does not make such symptoms less clinically

- ASCVD risk related to elevated atherogenic lipoproteins should be addressed.
- Non-statin therapy may be required for patients who cannot reach therapeutic objectives with lifestyle and maximal tolerated statin therapy

The main modalities available in the US for lowering atherogenic lipoprotein concentration include:

- Lifestyle therapies
- Statins
- Ezetimibe (cholesterol absorption inhibitor)
- PCSK9 inhibitors (monoclonal antibody and small interfering RNA [siRNA])
- Bile acid sequestrants
- Bempedoic acid (ATP citrate lyase inhibitor)
- Fibrates
- Icosapent ethyl

Reference: NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient. J Clin Lipid 2022;13:41

Bottom Lines

- Measuring Apo B has many practical and theoretical benefits in ASCVD risk assessment
- As far as I can tell, no RCTs targeting Apo B have been completed
- As of now, I agree with the ACC AHA that measuring Apo B might be useful in those in whom 1) are at intermediate risk of ASCVD and 2) Cannot get CAC scoring
- CAC scoring can be used to de-risk patients who otherwise might be candidates for lifelong statin Rx | although this still remains a bit of an open question
- Many studies have demonstrated that the frequency of symptoms reported from statin use are similar to symptoms reported from placebo use
- It appears that up to ~ 50% of patients who participate in N-of-1 (open label) trials resume statin therapy
- Although statin intolerance remains a challenging clinical scenario – the nocebo effect has been demonstrated to be present in many intolerant patients
- Several strategies can be employed to improve adherence, if these fail, non-stain therapies are available to decrease CV risk

Appendix | Supplemental Articles

These are other recent studies looking at ADE from statin use, and in general all are consistent with the general safety of statins. And recall these drugs continue to demonstrate improved MACEs and in some populations all-cause mortality

12. Statin Use Not Assoc with Cognitive Decline

Background: The neurocognitive effect of statins in older adults remain uncertain.
Objectives: The aim of this study was to investigate the associations of statin use with cognitive decline and incident dementia among older adults.
Methods: This analysis included 18,846 participants ≥65 years of age in a randomized trial of aspirin, who had no prior cardiovascular events, major physical disability, or dementia initially and were followed for 4.7 years. Outcome measures included incident dementia and its subclassifications (probable Alzheimer's disease, mixed presentations); mild cognitive impairment (MCI) and its subclassifications (MCI consistent with Alzheimer's disease, other MCI); and changes in domain-specific cognition, including global cognition, memory, language and executive function, psychomotor speed, and the composite of these domains. Associations of baseline statin use versus nonuse with dementia and MCI outcomes were examined using Cox proportional hazards models and with cognitive change using linear mixed-effects models, adjusting for potential confounders. The impact of statin lipophilicity on these associations was further examined, and effect modifiers were identified.
Results: Statin use versus nonuse was not associated with dementia, MCI, or their subclassifications or with changes in cognitive function scores over time ($p > 0.05$ for all). No differences were found in any outcomes between hydrophilic and lipophilic statin users.

Baseline neurocognitive ability was an effect modifier for the associations of statins with dementia (p for interaction < 0.001) and memory change (p for interaction = 0.02).
Conclusions: In adults ≥65 years of age, statin therapy was not associated with incident dementia, MCI, or declines in individual cognition domains. These findings await confirmation from ongoing randomized trials.
Reference: Effect of Statin Therapy on Cognitive Decline and Incident Dementia in Older Adults. J Am Coll Cardiol . 2021 Jun 29;77(25):3145-3156.

13. Stain Use is Assoc with DM

Importance: Statin therapy has been associated with increased insulin resistance; however, its clinical implications for diabetes control among patients with diabetes is unknown.
Objective: To assess diabetes progression after initiation of statin use in patients with diabetes.
Design, setting, and participants: This was a retrospective matched-cohort study using new-user and active-comparator designs to assess associations between statin initiation and diabetes progression in a national cohort of patients covered by the US Department of Veterans Affairs from fiscal years 2003-2015. Patients included were 30 years or older; had been diagnosed with diabetes during the study period; and were regular users of the Veterans Affairs health system, with records of demographic information, clinical encounters, vital signs, laboratory data, and medication usage.
Interventions: Treatment initiation with statins (statin users) or with H2-blockers or proton pump inhibitors (active comparators).
Main outcomes and measures: Diabetes progression composite outcome comprised the following: new insulin initiation, increase in the number of glucose-lowering medication classes, incidence of 5 or more measurements of blood glucose of 200 mg/dL or greater, or a new diagnosis of ketoacidosis or uncontrolled diabetes.
Results: From the 705 774 eligible patients, we matched 83 022 pairs of statin users and active comparators; the matched cohort had a mean (SD) age of 60.1 (11.6) years; 78 712 (94.9%) were men; 1715 (2.1%) were American Indian/Pacific Islander/Alaska Native, 570 (0.8%) were Asian, 17 890 (21.5%) were Black, and 56 633 (68.2 %) were White individuals. Diabetes progression outcome occurred in 55.9% of statin users vs 48.0% of active comparators (odds ratio, 1.37; 95% CI, 1.35-1.40; P < .001). Each individual component of the composite outcome was significantly higher among statin users. Secondary analysis demonstrated a dose-response relationship with a higher intensity of low-density lipoprotein-cholesterol lowering associated with greater diabetes progression.
Conclusions and relevance: This retrospective matched-cohort study found that statin use was associated with diabetes progression, including greater likelihood of insulin treatment initiation, significant hyperglycemia, acute glycemic complications, and an increased number of prescriptions for glucose-lowering medication classes. The risk-benefit ratio of statin use in patients with diabetes should take into consideration its metabolic effects.
Reference: Association of Statin Therapy Initiation With Diabetes Progression: A Retrospective Matched-Cohort Study. JAMA Intern Med. 2021 Dec 1;181(12):1562-1574.

14. Rechallenge with statin (same or different) improves statin adherence

Background: Strategies to improve patients' tolerance of and adherence to statins may enhance the effectiveness of dyslipidemia treatment in those at risk for cardiovascular disease (CVD).
Purpose: To assess the benefits and harms of interventions to improve statin adherence in patients at risk for CVD.
Data Sources: MEDLINE, EMBASE, PubMed, and the Cochrane Library from December 2013 through May 2019 (English language only).
Study Selection: Systematic reviews (SRs), randomized controlled trials (RCTs), and cohort studies that addressed interventions for improving statin tolerance and adherence.
Data Extraction: One investigator abstracted data and assessed study quality, and a second investigator checked abstractions and assessments for accuracy.
Data Synthesis: One SR, 1 RCT, and 4 cohort studies were included. The SR found that intensified patient care improved adherence and decreased levels of total serum cholesterol and low-density lipoprotein cholesterol (LDL-C) at 6 months or more of follow-up. Compared with statin treatment discontinuation, nondaily statin dosing lowered total cholesterol and LDL-C levels. One large cohort study suggested that more than 90% of patients who discontinued statin treatment could be rechallenged with the same or a different statin and be adherent 1 year after a statin-related adverse event led to discontinuation. Two small cohort studies reported that more than 90% of patients who were previously intolerant to statins and who had low baseline levels of vitamin D were able to adhere to statins 1 year after vitamin D supplementation.
Limitation: This is a qualitative synthesis of new evidence with existing meta-analyses, and studies had several methodological shortcomings.
Conclusion: Although the strength of evidence for most interventions was low or very low, intensified patient care and rechallenge with the same or a different statin (or a lower dose) seem to be favorable options for improving statin adherence.
Reference: Interventions to Improve Statin Tolerance and Adherence in Patients at Risk for Cardiovascular Disease. Ann Intern Med 2020 Nov 17;173(10):806-812.

15. Statin use assoc with ↓ in All Cause and Disease Specific Mortality in Veterans > 75

Importance: Data are limited regarding statin therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in adults 75 years and older.
Objective: To evaluate the role of statin use for mortality and primary prevention of ASCVD in veterans 75 years and older.
Design, Setting, and Participants: Retrospective cohort study that used Veterans Health Administration (VHA) data on adults 75 years and older, free of ASCVD, and with a clinical visit in 2002-2012. Follow-up continued through December 31, 2016. All data were linked to Medicare and Medicaid claims and pharmaceutical data. A new-user design was used, excluding those with any prior statin

use. Cox proportional hazards models were fit to evaluate the association of statin use with outcomes. Analyses were conducted using propensity score overlap weighting to balance baseline characteristics.
Exposures: Any new statin prescription.
Main Outcomes and Measures: The primary outcomes were all-cause and cardiovascular mortality. Secondary outcomes included a composite of ASCVD events (myocardial infarction, ischemic stroke, and revascularization with coronary artery bypass graft surgery or percutaneous coronary intervention).
Results: Of 326 981 eligible veterans (mean [SD] age, 81.1 [4.1] years; 97% men; 91% white), 57 178 (17.5%) newly initiated statins during the study period. During a mean follow-up of 6.8 (SD, 3.9) years, a total 206 902 deaths occurred including 53 296 cardiovascular deaths, with 78.7 and 98.2 total deaths/1000 person-years among statin users and nonusers, respectively (weighted incidence rate difference [IRD]/1000 person-years, –19.5 [95% CI, –20.4 to –18.5]). There were 22.6 and 25.7 cardiovascular deaths per 1000 person-years among statin users and nonusers, respectively (weighted IRD/1000 person-years, –3.1 [95 CI, –3.6 to –2.6]). For the composite ASCVD outcome there were 123 379 events, with 66.3 and 70.4 events/1000 person-years among statin users and nonusers, respectively (weighted IRD/1000 person-years, –4.1 [95% CI, –5.1 to –3.0]). After propensity score overlap weighting was applied, the hazard ratio was 0.75 (95% CI, 0.74-0.76) for all-cause mortality, 0.80 (95% CI, 0.78-0.81) for cardiovascular mortality, and 0.92 (95% CI, 0.91-0.94) for a composite of ASCVD events when comparing statin users with nonusers.
Conclusions and Relevance: Among US veterans 75 years and older and free of ASCVD at baseline, new statin use was significantly associated with a lower risk of all-cause and cardiovascular mortality. Further research, including from randomized clinical trials, is needed to more definitively determine the role of statin therapy in older adults for primary prevention of ASCVD.
Reference: Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. JAMA 2020 Jul 7;324(1):68-78.

#16 CAC Scoring of marginal benefit

Clinical Question: Does adding a coronary artery calcium score to other means of determining risk of cardiovascular disease provide additional benefit?
Bottom Line: The CACS, when added to traditional risk assessment for CVD in asymptomatic adults to prevent a CVD event, provides little additional tweaking that results in actionable information. It will move some people calculated to be at high risk into a low-risk category, which may be of slight benefit, but it will also move some low-risk people into a higher risk category. It also comes with costs, including — I didn't know this — radiation exposure that is 17-times higher than a posterior anterior/lateral set of chest x-rays. (LOE = 1a)
Study Design: Meta-analysis (other)
Funding: Government
Setting: Not applicable
Allocation: Unknown
Synopsis: The authors of this meta-analysis identified 6 cohort studies (N = 17,961 patients) that assessed the value of adding a coronary artery calcium score (CACS) to a standard cardiovascular disease (CVD) risk equation. These studies were conducted in the United States (3), the Netherlands (1), Germany (1), and South Korea (1). The rates of cardiovascular events in the studies ranged from 0.9% to 9.4%. Two researchers independently screened the studies, extracted the data, and assessed for risk of bias, which was generally low for the included studies. The concordance statistic (C-statistic) assesses the ability of a risk factor, in this case, CACS, to predict outcome. Overall, the risk calculators (such as the Framingham Risk Score) had good, but not great, predictive validity before the CACS was added (C-statistic = 0.693 - 0.80). Adding the CACS only increased the C-statistic an additional 0.036, on average. Although the number of events was small, of the participants classified at low risk by the calculator who were bumped out to a higher risk level by CACS, most (86% to 96%) did not have a CVD event over the subsequent 5 to 10 years. Patients whose high risk by calculation who were downgraded by CACS similarly did not experience a CVD event (91% to 99%) during follow-up. Though not formally studied, CACS determination could carry risks such as cost, incidental findings, radiation exposure, and labeling.
Reference: Evaluation of the incremental value of a coronary artery calcium score beyond traditional cardiovascular risk assessment: a systematic review and meta-analysis. JAMA Intern Med. Published online April 25, 2022. doi: 10.1001/jamainternmed.2022.1262.