Top 20 POEMs of 2019

Patient Oriented Evidence that Matters

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HYPERTENSION

1. Bedtime instead of morning ingestion of hypertension meds = significantly more reduction in cardiovascular disease risk

Hermida RC, Crespo JJ, Dominguez-Sardina M, et al, for the Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. European Heart J 2019 Oct 22. pii: ehz754. [Epub ahead of print]

Question: Does bedtime ingestion instead of morning ingestion of hypertension medications produce better cardiovascular disease risk reduction in adults with hypertension?

Bottom line: This study found a significant reduction in mortality and morbidity among patients who took their once-daily antihypertensive medications at bedtime instead of on awakening. Although no significant difference occurred in compliance rates between bedtime and awakening ingestion times in this study, individual experiences may differ in clinical practice.

Design: Randomized controlled trial (single-blinded); LOE: 1b-
Setting: Outpatient (primary care)
Synopsis: These investigators identified 19,168 adults, 18 years or older, who met standard criteria for hypertension that required prescription treatment to lower blood pressure (BP). The study participants randomly received (uncertain concealment) assignment to the intervention group and were told to ingest the entire daily dose of one or more prescribed BP-lowering medications at bedtime, or to the control group and were told to ingest the entire daily dose on awakening. Clinicians provided care without restriction to choice of BP-lowering medication approved for once-daily dosing (eg, angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, calcium channel blocker, beta-blocker, and/or diuretic). Statins, aspirin, and diabetes medications were also prescribed as needed and ingested as recommended. Individuals masked to treatment group assignment assessed outcomes, including the primary composite outcome of myocardial infarction, coronary revascularization, heart failure, stroke, and CVD death. Complete follow-up occurred for more than 99% of participants at a median of 6.3 years.

Using intention-to-treat analysis, significantly fewer patients in the bedtime group experienced the primary cardiovascular disease outcome (n = 1752 total) compared with the awakening group (adjusted HR = 0.55; 95% CI 0.50 - 0.61; number needed to treat = 20.3; 17.4 - 24.3). Adverse events occurred similarly in both groups. Similarly poor adherence was reported at any visit during follow-up in both groups (approximately 3%). (DS)

2. Fully automated blood pressure measurement is the way to go in the office

Roerecke M, Kaczorowski J, Myers MG. Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension. A systematic review and meta-analysis. JAMA Intern Med 2019;179(3):351-362.

Question: Is fully automated blood pressure measurement more accurate than manual sphygmomanometry?

Bottom line: There are 2 takeaways and a recommendation from this analysis of in-office automated blood pressure measurement. The takeaways: (1) Automated measurement aligns better with ambulatory blood pressure monitoring, the best predictor of cardiovascular events, than manual measurement; and (2) manual readings are an average 13.4 to 14.5 mm Hg (systolic) higher than daytime ambulatory or automated readings in patients with hypertension. The recommendation: Since the recent guidelines from the American College of Cardiology/American Heart Association are based on automated readings, follow them only if you switch from the squeeze bulb to the machine.

Design: Meta-analysis (other); LOE: 1b
Setting: Various (meta-analysis)
Synopsis: The authors searched 3 databases, including the Cochrane Central Register of Controlled Trials, to identify studies that compared automated office blood pressure readings with standard or research-based manual measurement or ambulatory automated recording during awake hours (the latter used as the reference standard). The authors also searched reference lists of identified articles. They included papers in any language, 2 authors independently selected articles for inclusion, and a single investigator extracted data. Automated measurement had be performed without anyone activating the machine and used 3 to 5 readings separated by 1-minute to 2-minute intervals. In 31 studies of 9279 participants, the pooled mean differences between routine measurement and awake ambulatory measurements were 13.4 mm Hg systolic and 5.9 mm Hg diastolic. There was no difference between ambulatory and automated blood pressure. The difference between manual and automated blood pressures was 14.5 mm Hg systolic in patients with hypertension. There was a great deal of heterogeneity among studies for all outcomes that could not be explained by any of the variables available to the researchers. There was no evidence of publication bias. (AS)

BEHAVIORAL MEDICINE

3. Multiple drugs in several classes are effective and well tolerated in patients with generalized anxiety disorder

Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019;393(10173):768-777.

Question: Which medications are effective in treating patients with generalized anxiety disorder?

Bottom line: In this network meta-analysis, the drugs that had the best combination of effectiveness and tolerability in patients with generalized anxiety disorder (GAD) were duloxetine, pregabalin, venlafaxine, and escitalopram. Quetiapine, paroxetine, and

benzodiazepines were effective, but poorly tolerated. However, none of the effect sizes reported appear to be clinically meaningful.

Design: Meta-analysis (randomized controlled trials); LOE: 1a
Setting: Various (meta-analysis)
Synopsis: These authors searched more databases and registries than I knew existed to identify randomized trials that compared an active drug with a placebo or another active drug in treating patients with GAD. They excluded studies of patients with refractory GAD and any studies with tolerability run-in periods (YES! Thank you!). The researchers used the Cochrane Collaboration Risk of Bias Tool to assess each of the included studies. Ultimately, they included 89 studies of more than 25,000 patients and 22 different drugs from multiple drug classes. After extracting the data, the authors conducted a network meta-analysis to estimate the relative comparative effectiveness of each drug, as well as its tolerability. Most of the studies were double-blind and funded by industry. Studies from China (n = 16) were more likely to be have a higher risk of bias, and investigator-initiated studies were more likely to use an active comparator. Seven studies recruited patients older than 65 years. The median follow-up was 8 weeks and none were longer than 26 weeks. Overall, the most effective commercially available drugs, in order of effectiveness were bupropion, quetiapine, duloxetine, mirtazapine, hydroxyzine, sertraline, pregabalin, venlafaxine, escitalopram, fluoxetine, buspirone, "benzodiazepine," paroxetine, and citalopram. Several other agents did not statistically significantly decrease anxiety scores: imipramine, maprotiline, opipramol, tiagabine, vilazodone, and vortioxetine. However, several of the top performers were also associated with higher study discontinuation: quetiapine, paroxetine, benzodiazepines. The drugs with the best combination of effectiveness and tolerability were duloxetine, pregabalin, venlafaxine, and escitalopram. Finally, the magnitude of reduction in the best performers was only in the range of 2 to 3 points on a 56-point scale. Generally, 15% to 20% reductions are considered to be clinically meaningful, which would be 8 to 11 points in this case. (HB)

4. Primary care patients often fail to disclose symptoms like anxiety, depression, fatigue, and sexual or relationship problems

Paskins Z, Sanders T, Croft PR, Green J, McKinley R, Hassell AB. Non-disclosure of symptoms in primary care: an observational study. Fam Pract 2018;35(6):706-711.

Question: How often do patients fail to disclose their symptoms during a visit to their primary care physician?

Bottom line: Patients often fail to disclose symptoms, including some they may consider to be sensitive, such as anxiety, depression, and sexual or interpersonal problems. It is important that, as primary care physicians, we remain aware of this, look for cues, and make sure patients know that they have permission and a safe space to discuss these issues with us.

Design: Cross-sectional; LOE: 3b
Setting: Outpatient (primary care)
Synopsis: These researchers approached 252 adults scheduled to visit 1 of 15 English general practitioners (GPs) and asked for permission to videotape the encounter. Ultimately, 190 agreed and were videotaped. Each patient was interviewed before the visit and asked about the main reason for their visit, the presence of any of 11 groups of symptoms in a checklist, and whether they planned to address the symptom with their physician. Symptoms present in at least half included joint pain, back or neck ache, tiredness or a sleep problem, and cough/cold/breathing

difficulty. Of the 188 patients who identified a main reason for the consultation, 185 discussed it with their physician. However, among the 139 patients who identified an intention to discuss at least one symptom from the checklist, 43 patients failed to disclose 67 symptoms to their physician during the visit. Symptoms that patients identified on the checklist but most often indicated they did not want to talk to their physician about included stress; worries or sadness; tiredness or sleep problems; problems passing urine; headache; and intimate or personal problems. Among those who expressed an intention to discuss the problem with their physician, they most often did not follow through with a mention of tiredness or sleep problems and intimate or personal problems. The fact that patients and GPs knew that they were part of a study on patient-physician communication means that, if anything, the findings may understate the problem in the real world. (ME)

5. Do not change antidepressant treatment early based on a lack of response

De Vries YA, Roest AM, Bos EH, Burgerhof JGM, van Loo HM, de Jonge P. Predicting antidepressant response by monitoring early improvement of individual symptoms of depression: individual patient data meta-analysis. Br J Psychiatry 2019; 214(1):4-10.

Question: Does a lack of early symptom improvement in patients treated for depression predict treatment failure?

Bottom line: Don't be in a hurry to change treatment in patients with severe depression who do not respond to treatment within the first 2 weeks. Early response to treatment predicts eventual response or remission, but a lack of early response does not predict treatment failure. Approximately one third of patients who do not show an early response will respond by 6 weeks. No individual symptom response predicts eventual improvement.

Design: Meta-analysis (randomized controlled trials); LOE: 1a
Setting: Various (meta-analysis)
Synopsis: These researchers used individual patient data derived from 30 studies of the treatment of severe major depressive disorder with a second-generation antidepressant. Overall, they had data on 2184 patients who received a placebo and 6058 who received an antidepressant. By 6 weeks of treatment, approximately 50% of treated patients had responded, with 32% achieving remission of symptoms. By 12 weeks, the rate was up to approximately 68% response with 49% achieving remission. Patients with early improvement—by 2 weeks—were likely to respond by 6 weeks, but almost 33% of patients without early improvement responded by 6 weeks and 43% of them responded by 12 weeks. No individual symptom response predicted eventual response or remission. (AS)

INFECTIONS

6. Normal vitals and lung exam results rule out CAP in adults with acute respiratory infection

Marchello CS, Ebell MH, Dale AP, Harvill ET, Shen Y, Whalen CC. Signs and symptoms that rule out community-acquired pneumonia in outpatient adults: A systematic review and meta-analysis. J Am Board Fam Med 2019;32(2):234-247.

Clinical question: What signs and symptoms are most useful for excluding the diagnosis of

pneumonia in community-dwelling adults with an acute respiratory infection?

Bottom line: Community-dwelling adults who present to a primary care office with acute respiratory infection symptoms but normal vital signs and normal findings on a pulmonary examination have only a 0.4% likelihood of community-acquired pneumonia (CAP).

Study design: Systematic review
Setting: Various (meta-analysis)

Synopsis: Identifying signs and symptoms that reliably rule out CAP may help reduce the overuse of radiography and/or laboratory testing. These investigators systematically searched MEDLINE and reference lists of pertinent articles for studies that used a clinical decision rule to diagnose CAP in the outpatient setting. Eligible criteria included the use of either a chest x-ray or computed tomography as the reference standard for either all enrolled patients or a random/systematic sample of the enrolled patients. In addition, only studies that recruited adults or adolescents in an outpatient setting, including the emergency department, were included. Two individuals independently reviewed potential studies for inclusion criteria and methodologic quality using standard criteria. The resolution of any disagreements occurred after consensus discussion with a third reviewer. A total of 12 studies met inclusion criteria, of which 6 were performed in an emergency department setting and 6 in a primary care setting. Sample sizes ranged from 246 to 2820 patients. Six studies were found to be at low risk of bias; the remaining 6 were at moderate risk of bias. The combination of normal vital signs (temperature, respiratory rate, and heart rate) plus normal findings on the pulmonary examination reliably excluded CAP (sensitivity = 0.96; 95% CI 0.92 - 0.28; negative likelihood ratio = 0.10; 0.07 - 0.13).

7. Five days of penicillin for strep throat is equal to 10 days

Skoog Ståhlgren GS, Tyrstrup M, Edlund C, et al. Penicillin V four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study. BMJ 2019;367:l5337.

Question: Can strep throat in children and adults be treated with 5 days of oral penicillin?

Bottom line: Five days of 800 mg penicillin 4 times a day produced results not worse than (ie, noninferior to) 10 days of 1000 mg penicillin 3 times a day, with shorter symptom duration. This is not the first study to show similar benefits with a shorter duration of oral augmentin/cephalosporin or amoxicillin.

Allocation: (Concealed)

Design: Randomized controlled trial (single-blinded); LOE: 2b
Setting: Outpatient (primary care)
Synopsis: The investigators enrolled 317 adults and 105 children (6 years and older) from 17 primary care centers in Sweden. Eligible patients had to have at least 3 Centor criteria and a positive rapid antigen test result for group A streptococcus. Using concealed allocation, patients were randomly assigned to receive either 800 mg penicillin 4 times a day for 5 days or 1000 mg penicillin 3 times a day for 10 days. This was an open-label trial, meaning that both patients and their clinicians were aware of the treatment the patient received. However, the researchers who analyzed the data were masked to treatment until the results were assembled. Clinical cure,

defined as complete recovery without major residual symptoms or clinical findings, was assessed 5 days to 7 days after the completion of treatment; that is, on day 10 to day 12 in the 5-day treatment group and on day 15 to day 17 in the 10-day treatment group. This timing of assessment could possibly favor better results with longer treatment. In the per-protocol analysis (patients who completed treatment), cure rates at 5-7 days post treatment were 89.6% in the 5-day group and 93.3% in the 10-day group. Results were similar when using intention-to-treat analysis. Patients receiving the higher daily dose/shorter duration had quicker symptom resolution. Bacterial cure rates were higher with 10 days of treatment but there was no difference in complication rates or new episodes of tonsillitis at the 3-month follow-up. Adverse events such as diarrhea, nausea, or vaginitis were more likely and lasted longer in the 10-day group. The study had a power of 85% to detect a greater than 10% difference between treatments if one existed. (AS)

8. It takes up to 3 weeks for 90% of respiratory infections to resolve in kids

Hay AD, Anderson E, Ingle S, Beck C, Hollingworth W. Respiratory tract infections in children in the community: prospective online inception cohort study. Ann Fam Med 2019;17(1):14-22.

Question: How long do colds last in children?

Bottom line: Most respiratory illnesses in children are mild and don't result in seeking medical care or missing school, but they can last as long as 3 weeks.

Design: Cohort (prospective); LOE: 1b-
Setting: Population-based
Synopsis: These researchers from the United Kingdom enrolled a cohort of 485 generally healthy children aged between 3 months and 15 years from February to July 2016. They recruited patients from the enrollment lists of practices located within 10 miles of Bristol. They excluded immunocompromised children and those with terminal illnesses. If the child had a respiratory illness, the researchers asked the parents to start the cohort once the symptoms resolved. Each week, the researchers sent an e-mail or text message asking whether the child had specific respiratory tract symptoms, such as rhinorrhea, earache, sore throat, or cough. If the child had any of these symptoms, the researchers asked the parent to provide daily online updates. They also asked the parents about missed school, medication use, consultations, and so forth. Based on the patient lists from the participating practices, participating children tended to be 2 years younger and less socioeconomically deprived than the nonparticipating children. During 5 months of follow up, parents reported 346 new respiratory infections in 259 children—53% of children had at least one new respiratory infection; the attack rate was 71% and afflicted kids averaged 1.3 infections during this short interval. The researchers report on 197 children's first illness. The median duration of illness was 9 days, but this is a skewed distribution with a long tail: It took 23 days for 90% of the children to recover. Approximately half the parents reported symptoms associated with lower respiratory infections and the presence of these symptoms was associated with longer duration. Sniffles tended to last, while earaches were of the shortest duration. Dry cough was most severe for the first 10 days, but also persisted for about 3 weeks. The parents had primary care consultations (office or telephone encounters) only 8% of the time, and only 9% of infections caused a missed day of school. As one might expect, the severity of symptoms was worse among those kids. Since a healthy chunk of the study period occurred in spring and summer, these numbers might be worse during fall and winter months. (HB)

PREVENTION

9. New zoster vaccine prevents more cases, but causes more sore arms

Tricco AC, Zarin W, Cardoso R, et al. Efficacy, effectiveness, and safety of herpes zoster vaccines in adults aged 50 and older: systematic review and network meta-analysis. BMJ 2018;363:k4029.

Question: Which herpes zoster vaccine is more effective?

Bottom line: The adjuvant recombinant subunit version (Shingrix) of the herpes zoster vaccine is much more effective than the live attenuated version (Zostavax). There's more to the story, however: Shingrix is much more likely to cause injection site pain. Unlike the live version, it requires 2 doses and—although not demonstrated in the trials—a few days of acute arm soreness might limit patients' enthusiasm for the required second dose, and both doses are required for an adequate immune response.

Design: Meta-analysis (other); LOE: 1a
Setting: Various (meta-analysis)
Synopsis: These researchers searched several databases, including the Cochrane Library, as well as trial registries and reference lists. They assembled 27 studies, mostly randomized controlled trials, that compared the effects of herpes zoster vaccination. The studies, ranging in size from 54 to 766,380 patients, comprised a total of more than 2 million patients. They used a network meta-analysis, which allowed them to compare the 2 forms of the vaccine against each other even though they weren't directly compared. Using this method of analysis, the live attenuated version did not decrease the likelihood of confirmed herpes zoster any more than placebo. However, the subunit vaccine was markedly more effective than both placebo and the live attenuated version (vaccine efficacy 85% vs the live version and 94% vs placebo). Not without cost, though: The subunit vaccine was almost twice as likely as the live version to cause injection site reactions and more likely than placebo to cause systemic adverse effects. (AS)

10. Statins are effective in the elderly, but data are limited for those without established vascular disease

Cholesterol Treatment Trialists' Collaboration, Armitage J, Baigent C, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 2019;393(10170):407-415.

Question: Are statins effective in patients older than 75 years?

Bottom line: Statins are effective in preventing major coronary events in patients older than 75 years, but this effect is exclusive to those with established vascular disease (ie, effective for secondary, not primary, prevention). This is consistent with the results from the ALLHAT trial, which also showed no benefit to primary prevention, and additionally showed a trend to harm in those older than 75 years.

Design: Meta-analysis (other); LOE: 1a
Setting: Various (meta-analysis)
Synopsis: The members of the Cholesterol Treatment Trialists’ Collaboration have pooled the patient level data from randomized trials of statins that evaluated low-density lipoprotein (LDL)

concentrations and included at least 1000 patients who were followed up for at least 2 years. These data from 28 studies and more than 186,000 total patients included more than14,000 patients 75 years or older (~ 8% of the total pool). The researchers followed up these patients for a median of 5 years. They used an intention-to-treat analysis to evaluate the main outcomes of major coronary events (nonfatal myocardial infarction or coronary death), coronary revascularization, stroke, cancers, and all-cause mortality. Among patients older than 75 years, 2.6% of statin-treated patients experienced a major coronary event each year compared with 3% of control patients (number needed to treat = 250 per year). The authors report there was a barely significant 13% relative reduction in cardiovascular events for every mmol/L reduction in LDL concentration (relative risk 0.82; 95% CI 0.70 - 0.96). However, the rate of revascularization and stroke was not significantly decreased with statins. The authors also found no effect of statins on incident cancers or cancer mortality. Finally, although the data were limited, patients without vascular disease at the time of enrollment experienced no significant reduction in events. (HB)

11. Low-dose aspirin does not prevent onset of cardiovascular disease in older adults (ASPREE)

McNeil JJ, Wolfe R, Woods RL, et al, for the ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379(16):1509-1518.

Question: Does low-dose aspirin prevent cardiovascular events and cardiovascular-related death in otherwise healthy older persons?

Bottom line: Low-dose aspirin does not reduce the likelihood that otherwise healthy older patients will experience a major cardiovascular event during nearly 5 years of follow-up.

Allocation: (Concealed)

Design: Randomized controlled trial (double-blinded); LOE: 1b
Setting: Population-based
Synopsis: The Aspirin in Reducing Events in the Elderly (ASPREE) trial 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. A separate report found no significant reduction in the composite of death, dementia, and disability. The current report looks at the composite outcome of fatal coronary heart disease, nonfatal myocardial infarction, stroke, and hospitalization for heart failure. This is a broad composite, so it is important to look at

individual components of the outcome. In this case, there was no difference between groups regarding the composite or any of the individual components. 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). (ME)

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

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.

Question: Does aspirin improve disability-free survival in an otherwise healthy older person?

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.

Allocation: (Concealed)

Design: Randomized controlled trial (double-blinded); LOE: 1b
Setting: Population-based
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). (ME)

13. Both benefits and harms for low-dose aspirin in patients with diabetes mellitus (ASCEND)

The ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379(16):1529-1539.

Question: What are the benefits and harms of low-dose aspirin in adults with diabetes mellitus?

Bottom line: The 7740 patients who took low-dose aspirin experienced 51 fewer vascular deaths, nonfatal myocardial infarctions (MIs), or nonfatal ischemic strokes; 29 fewer transient ischemic attacks (TIAs); and 44 fewer revascularizations than patients who took placebo over a mean of 7.4 years. This is balanced by an additional 69 major bleeding episodes during that period, with no effect on vascular or all-cause deaths, and no difference in the incidence of cancer.

Allocation: (Concealed)

Design: Randomized controlled trial (double-blinded); LOE: 1b
Setting: Outpatient (any)
Synopsis: This British study recruited adults 40 years and older with diabetes mellitus, no known cardiovascular disease, no contraindications to aspirin, and no major comorbidity that would keep them from participating in the study for at least 5 years. After a placebo run-in period to assure adherence, 15,480 participants were randomized to receive aspirin 100 mg once daily or matching placebo. They were also randomized to receive an omega-3 fatty acid capsule or placebo; those results are reported separately. The groups were balanced at the start of the study: the patients had a mean age of 63 years, 63% were men, and 96% were white. Almost all (94%) had type 2 diabetes mellitus. A validated risk score determined that approximately 40% of participants were at low risk of vascular events (< 5% at 5 years), 40% had a 5-year risk of 5% to 10%, and the remainder were at high risk. As the trial was ongoing, the authors added TIA to the original primary composite efficacy outcome of vascular death, nonfatal MI, or nonfatal stroke (excluding intracranial hemorrhage). The primary safety outcome was a composite of intracranial hemorrhage, intra-ocular hemorrhage that threatens sight, gastrointestinal bleeding, or any other serious bleeding event. After a mean follow-up of 7.4 years, 99% of patients had complete follow-up data, with outcomes adjudicated for more than 90% by a committee masked to treatment assignment. The authors also looked at the effect of adding revascularization to the composite efficacy outcome. There was no difference between groups in the original efficacy outcome of vascular death, nonfatal MI, and nonfatal ischemic stroke (7.0% with aspirin vs 7.6% with placebo; hazard ratio [HR] 0.92, 95% CI 0.82 - 1.03). When you add TIA to the composite outcome, the difference between groups is statistically significant (8.5% vs 9.6%; HR 0.88, 0.79 – 97; number needed to treat [NNT] = 90 for 7.4 years). Adding revascularization to the original efficacy outcome had a similar result (10.8% vs 12.1%; HR 0.88, 0.80 - 0.97; NNT = 77 for 7 years). When examining results stratified by vascular risk, those at moderate and higher vascular risk also experienced more major bleeding events (8.9 - 9.6 vs 2.8 per 5000 person-years in the low-risk group). The number of serious vascular events avoided per 5000 person years was 5.7 in the low-risk group, 11.2 in the moderate-risk group, and only 4.9 in the high-risk group. For the composite harm outcome, there was a significantly increased risk of major bleeding, primarily due to more serious gastrointestinal and other bleeds (4.1% vs 3.2%; HR 1.29, 1.09 - 1.52; number needed to treat to harm = 111 over 7 years). However, there was no difference in fatal bleeding events or hemorrhagic strokes. There was no difference in the incidence of cancer (11.6% for aspirin vs 11.5% for placebo), including for gastrointestinal cancers (2.0% vs 2.0%). There was no significant differences between groups in all-cause mortality or in vascular deaths. (ME)

14. Fasting and nonfasting lipid levels similarly predict CVD risk

Mora S, Chang CL, Moorthy MV, Sever PS. Association of nonfasting vs fasting lipid levels with risk of major coronary events in the Anglo-Scandinavian cardiac outcomes trial--lipid lowering arm. JAMA Intern Med 2019;179(7):898-905.

Question: Are fasting lipid levels more predictive of cardiovascular outcomes than nonfasting lipid levels?

Bottom line: Guidelines recommend checking lipid levels in nonfasting patients. They are easier to obtain and, as this study found, are equally predictive of subsequent cardiac events. Although triglyceride levels may be higher in nonfasting patients, cholesterol levels will be similar whether the patient was fasting or not.

Design: Cohort (retrospective); LOE: 2c
Setting: Outpatient (any)
Synopsis: This study looked at 8270 patients enrolled in a clinical trial of cholesterol lowering. The patients were between the ages of 40 years and 79 years with hypertension and a total untreated cholesterol level of less than 250 mg/dL (6.5 mmol/L) with 3 additional risk factors for cardiovascular disease. The authors obtained nonfasting and fasting lipid levels, 4 weeks apart, during the baseline period of the study. The average fasting and nonfasting total cholesterol and HDL cholesterol levels were similar. Triglyceride levels were modestly higher (25 mg/dL; 0.28 mmol/L) when measured in nonfasting patients. The hazard ratios, which in this case measured of the cumulative risk of having a major coronary event within 3.3 years, were similarly associated with fasting and nonfasting cholesterol levels. Results were similar for patients with and without previous cardiovascular disease and in treated and nontreated patients. (AS)

CANCER SCREENING

15. FIT has similar yield as colonoscopy for colorectal cancer and advanced adenoma over 10 years

Zorzi M, Hassan C, Capodaglio G, et al. Long-term performance of colorectal cancer screening programmes based on the faecal immunochemical test. Gut 2018;67(12):2124-2130.

Question: What is the yield of a screening program based on fecal immunochemical testing every 2 years for 10 years?

Bottom line: Over a 10-year period, the rates of detection of colorectal cancer (CRC) and advanced adenomas using fecal immunochemical testing (FIT) are similar to those seen in studies of screening colonoscopy. This is reassuring, but it does not prove that FIT reduces morbidity and mortality due to CRC as effectively as colonoscopy. Modeling concludes that a FIT-based screening program will result in half as many colonoscopies as a program based on colonoscopy, a significant reduction in cost, burden, and harm of screening.

Design: Cohort (prospective); LOE: 2b
Setting: Population-based
Synopsis: The 2 most widely recommended strategies for CRC screening are FIT and colonoscopy. Several trials are currently underway to compare these approaches, with cancer-specific mortality as the primary outcome. Until then, we have to rely on observational studies and modeling to understand the benefit of each approach. Although colonoscopy is more sensitive than FIT, especially for the detection of advanced adenomas, what matters is performance over a long-term screening program, not one-time accuracy. This study reports the

results of 5 rounds of biennial FIT in a screeening population aged 50 to 69 years in the Veneto region of northern Italy. Not surprisingly, the rate of detection of CRC was highest in the first round of screening when prevalent lesions were detected (3.3/1000 persons), declining in subsequent rounds and stabilizing after the third round (~1/1000 persons). Between rounds 3 and 6, the CRC detection rate declined slightly from 0.95 to 0.84 per 1000. A similar pattern was seen for advanced adenomas, declining from 15.9 per 1000 persons to approximately 10 per 1000 persons in subsequent rounds. Over the 10-year study period, the cumulative rate of positive FIT results was 25% for men and 17.6% for women. The cumulative rate for advanced adenoma was 60 per 1000 persons, and for CRC was 8.5 per 1000 persons. These rates are similar to those seen in studies of colonoscopy in both Italy and the United States. (ME)

16. Results of fecal immunochemical tests for colorectal cancer screening not affected by NSAIDs, aspirin, or anticoagulants

Nieuwenburg SA, Vuik FE, Kruip MJ, Kuipers EJ, Spaander MC. Effect of anticoagulants and NSAIDs on accuracy of faecal immunochemical tests (FITs) in colorectal cancer screening: a systematic review and meta-analysis. Gut 2019;68(5):866-872

Question: Are the modern fecal immunochemical tests for occult blood in the stool less accurate in patients who are taking aspirin, an anticoagulant, or a nonsteroidal anti-inflammatory drug?

Bottom line: The use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral anticoagulants have no clinically important effects on the positive predictive value of the fecal immunochemical test (FIT) in a screening population.

Design: Systematic review; LOE: 1a
Setting: Various (meta-analysis)
Synopsis: Prevous research has shown that approximately 6.2% of screening FIT results are positive, with a positive predictive value (PPV) of 35% to 55%. These authors wondered whether the use of something that can make you bleed would reduce the PPV by making benign lesions more likely to bleed (leading to more false-positive results), or whether it would increase the PPV by making precancerous and malignant lesions more likely to bleed? They did a careful search of the literature and identified 8 studies with 2022 patients that compared the accuracy of the FIT in a screening population of patients taking an oral anticoagulant or an NSAID with those not taking either drug. Of the 8 studies, all but one were done in Europe (the eighth was in Hong Kong), most used a FIT cutoff of 15 to 20 mcg Hb/g. Six studies included aspirin users, 4 included oral anticoagulant users, and 1 included NSAID users (3 of the studies included more than one medication). The authors found no consistent effect on PPV among users and nonusers of oral anticoagulants and NSAIDs, and in general the differences were small. For example, the pooled PPV for advanced neoplasia was 38.2% in aspirin/NSAID users and 39.4% in nonusers. The PPVs for colorectal cancer in oral anticoagulant users and nonusers were 5.7% and 6.2%, respectively. And the PPVs for advanced neoplasia in oral anticoagulant users and nonusers were 37.6% and 40.3%, respectively. (ME)

17. Colorectal cancer risk is increased in first-degree relatives

Tian Y, Kharazmi E, Sundquist K, Sundquist J, Brenner H, Fallah M. Familial colorectal cancer risk in half siblings and siblings: nationwide cohort study. BMJ 2019;364:l803.

Question: What is the risk of colorectal cancer in family members of patients with colorectal cancer?

Bottom line: People with a first-degree relative (parent, sibling, or half sibling) with colorectal cancer (CRC) or with 2 second-degree relatives with CRC are at increased likelihood of developing CRC over their lifetime as compared with the general population (6% vs 4%). Having 2 or more siblings or a parent and sibling with CRC increases the risk to 9%.

Design: Cohort (prospective); LOE: 1b
Setting: Population-based
Synopsis: These authors used the Nationwide Swedish Cancer registry to identify 173,796 people born after 1958 who developed CRC, and crossed-referenced these patients with their first-degree and second-degree relatives using a multigeneration registry that connects people with their relatives, linking a total of more than 16 million people. By looking at a patient's parents they could calculate that patient's risk and by linking to his or her siblings they could look for the sibling's risk. These databases keep track of everyone who lived in Sweden over an average 33.6 years of follow-up. Over their lifetime, a person with either one first-degree relative (parent or sibling) or 2 second-degree relatives (grandparent, aunt, or uncle) with CRC has a risk of approximately 6% (1 in 17), a 60% increase in likelihood compared with people without a first-degree relative with CRC. A similarly increased risk was seen in half siblings (6%; 95% CI 1.3 - 1.8). People with both a parent and sibling or half sibling with CRC had a 3.6-fold increase in cumulative incidence (9%). Having only one second-degree relative with CRC showed a minor association with the risk of CRC. (AS)

MISCELLANEOUS

18. Risk of GI bleeding highest with rivaroxaban, lower with apixaban… and lowest with PPI cotherapy

Ray WA, Chung CP, Murray KT, et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. JAMA 2018;320(21):2221-2230.

Question: Which oral anticoagulants have the highest risk of causing upper gastrointestinal tract bleeding, and does cotherapy with a proton pump inhibitor lower that risk?

Bottom line: Among patients using oral anticoagulants alone, the risk of hospitalization for upper gastrointestinal tract (UGI) bleeding is highest with rivaroxaban (Xarelto) and lowest with apixaban (Eliquis). Cotherapy with a proton pump inhibitor (PPI) reduces the risk among patients using any oral anticoagulant.

Design: Cohort (retrospective); LOE: 2b
Setting: Outpatient (any)
Synopsis: The risk of serious UGI bleeding associated with individual anticoagulant drug choice (with or without PPI cotherapy) is uncertain. These investigators analyzed the US Medicare beneficiary files of patients, 30 years or older, who initiated oral anticoagulation treatment with apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto), or warfarin. The primary outcome of interest was hospitalization for UGI bleeding that is potentially preventable by PPI cotherapy, including esophagitis, peptic ulcer disease, and gastritis. Multiple analyses occurred to control for covariates, including cardiovascular disease, low-dose aspirin prophylaxis, frailty,

alcohol abuse, liver disease, history of previous UGI bleeding, current use of other medications that affect bleeding risk (eg, nonsteroidal anti-inflammatory drugs), and age/other demographic factors.

A total of 1,643,123 patients had 1,713,183 new episodes of oral anticoagulant treatment from January 1, 2011, through September 30, 2015. The mean age of the patients was 76.4 years and the indication for anticoagulation was atrial fibrillation for 74.9% of them. In patients receiving anticoagulant treatment without PPI cotherapy, the adjusted incidence of hospitalization for UGI bleeding was significantly higher in those who received rivaroxaban compared with those who received dabigatran, warfarin, or apixaban (144 per 10,000 person-years vs 120, 113, and 73, respectively). For patients receiving anticoagulant treatment with PPI cotherapy, the adjusted incidence of severe UGI bleeding was lower than without cotherapy for all anticoagulants (76/10,000 per year vs 115/10,000 per year; number needed to treat = 256), although still significantly highest with rivaroxaban. (DS)

19. Equivalent pain relief with different doses of ibuprofen

Motov S, Masoudi A, Drapkin J, et al. Comparison of oral ibuprofen at three single-dose regimens for treating acute pain in the emergency department: a randomized controlled trial. Ann Emerg Med 2019;74(4):530-537.

Question: In patients with acute pain, does a higher dose of ibuprofen produce greater pain relief?

Bottom line: Higher doses of ibuprofen for acute pain relief offer no more benefit at 60 minutes than a single 400-mg dose. The same has been shown for chronic treatment of osteoarthritis--an anti-inflammatory dose is not needed. Furthermore, another study showed equivalence between 200-mg and 400-mg doses of ibuprofen.

Allocation: (Concealed)

Design: Randomized controlled trial (double-blinded); LOE: 2b
Setting: Emergency department
Synopsis: These authors enrolled 225 adults who presented to a single emergency department with an acute painful condition (~75% with musculoskeletal pain). The average pain score was between 6 and 7 on a scale of 1 to 10, with higher scores indicating higher pain. Using concealed allocation, patients were randomly assigned to receive a single dose of ibuprofen, either 400 mg, 600 mg, or 800 mg. Using intention-to-treat analysis, pain scores after 60 minutes dropped to 4.36 to 4.50 in all 3 groups. The study had 80% power to find a difference of at least 1.3 points, if it existed, among the groups. (AS)

20. Exercise decreases falls and injuries in older people

De Souto Barreto P, Rolland Y, Vellas B, Maltais M. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults. A systematic review and meta-analysis. JAMA Intern Med 2019;179(3):394-405.

Question: In older patients, do exercise classes or a prescribed exercise regimen decrease the risk of falls, injuries, or more serious outcomes?

Bottom line: Regular moderate-intensity exercise 2 to 3 times per week can decrease the overall likelihood of falls and resulting injuries in older patients, but does not decrease the overall risk of hospitalization or decrease mortality.

Design: Meta-analysis (randomized controlled trials); LOE: 1a-
Setting: Various (meta-analysis)
Synopsis: These investigators searched 5 databases, including the Cochrane Central Register of Controlled Trials, to identify randomized long-term studies that evaluated the effect of exercise programs on important outcomes in patients at least 59 years of age (mean age 73.1 years). They included research in any language. Two researchers independently screened articles, abstracted the data, and assessed the risk of bias. Twenty-nine of the 46 identified studies evaluated multicomponent training (aerobic/strength/balance), though strength training and aerobic exercise alone were also studied. The most common program included moderate-intensity exercise for 50 minutes 3 times per week. Exercise significantly decreased the risk of falls and injurious falls, but did not affect the risk of multiple falls, hospitalization, or mortality. Fractures were less likely in the exercise group but not significantly so. The average attendance at exercise classes was 65%. The quality of the research was not good, with several validity risks and evidence of publication bias. Also, the authors may have combined apples and oranges—the baseline risks of a 59-year-old patient are much different from those of an over-70-year-old, and individual versus group exercise programs might not be equivalent. (AS)

GUIDELINES

ACCP guidelines for antithrombotics in atrial fibrillation

Lip GY, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest 2018;154(5):1121-1201.

Question: What are the most recent American College of Chest Physicians recommendations regarding antithrombotic therapy for patients with atrial fibrillation?

Bottom line: This is a huge document with hundreds of recommendations, but the headline is that a direct oral anticoagulant is now recommended for most patients with newly diagnosed atrial fibrillation. The American College of Cardiology/American Heart Association has also recently released guidelines that recommend direct oral anticoagulants for most patients (http://www.onlinejacc.org/sites/default/files/additional_assets/guidelines/AFib-Guidelines-Made-Simple-Tool.pdf).

Design: Practice guideline; LOE: 1a
Setting: Various (guideline)
Synopsis: This is the most recent iteration of the guidelines for the management of antithrombotic therapy from the American College of Chest Physicians. The authors based the guideline on systematic literature reviews, used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach to assess the strength of evidence, and then used a consensus Delphi-like process for drafting the final recommendations. Here are the key takeaway points: (1) Use the CHA₂DS₂-VASc score to assess the risk of stroke. Men with a score of 0 and women with a score of 1 are at low risk for stroke and do not require anticoagulation. (2) Men with a CHA₂DS₂-VASc

score of 1 or more and women with a score of 2 or more should be offered anticoagulation. (3) The guidelines recommend direct oral anticoagulants as the preferred agents (rather than vitamin K antagonists) for most patients with newly diagnosed atrial fibrillation, although this decision should be individualized. (4) The guidelines recommend against using aspirin or aspirin plus clopidogrel for antithrombotic prophylaxis for atrial fibrillation. (5) Use the HAS-BLED score to assess bleeding risk; if the score is 3 or higher look for ways to reduce risk, educate about what to watch for regarding bleeding, and consider following up more closely. (6) For patients currently taking warfarin, consider switching to a direct oral anticoagulant if they are in the INR range less than 65% of the time. (7) If patients are also taking aspirin, first make sure they really need it, then use a low dose (75 mg to 100 mg) and treat with a concomitant proton pump inhibitor. There are a total of 60 recommendations, but these are the ones most relevant to primary care practice. (ME)

ADA guideline on individualizing T2DM goals is paramount, according to experts

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41(12):2669-2701.

Question: What do European and US diabetes experts recommend regarding the management of adults with type 2 diabetes?

Bottom line: These expert-consensus recommendations attempt to shift responsibility and decision-making to where it belongs—with the patients. Rather than issuing diktats that identify treatment failure, the recommendations suggest making diabetes self-management education and support a cornerstone of the treatment approach. Another pillar of this new approach is selecting medication treatment according to which one is most likely to be taken regularly and over time by a particular patient. The third pillar continues to be metformin. If additional control is needed, the group suggests adding one or more oral hypoglycemic to the metformin. For patients with known heart disease, the panel suggests additional treatment with liraglutide (Victoza) or empagliflozin (Jardiance), or other medications in these categories. Sulfonylureas and glitazones remain less-expensive options.

Design: Practice guideline; LOE: 5
Setting: Various (guideline)
Synopsis: These guidelines represent expert consensus among members of 2 diabetes associations. The recommendations are rooted in a systematic review of recent literature, but the guideline writers ask us to trust them, rather than show us their review. As such, this document is more of a philosophy statement than rigorous evidence-linked guidance. All the recommendation writers have extensive ties to the pharmaceutical industry. Though they had input from a wide variety of specialists, all the writers are diabetes experts. The guidelines emphasize a move away from strict biochemical cutoffs to define treatment goals, instead they recommend treating each patient on the basis of their specific baseline risk, preferences and desires, and capabilities. As such, they emphasize the role of education aimed at making patients capable of self-management. Metformin continues to be the first-line treatment, with other medications chosen after a discussion with patients. Using recent new evidence from cardiovascular outcomes trials, the guideline authors suggest treating patients with heart disease with either a GLP-1 receptor agonist such as liraglutide or an SGLT2 inhibitor such as

empagliflozin, the latter category preferred for patients with heart failure or chronic kidney disease. Nutrition is key, though the authors recommend against a rigid approach. For readers who want more detail, the article is open access here and has several useful flow charts to help with decision-making. (AS)

American College of Physicians: mammography every 2 years between the ages 50 and 74 years

Qaseem A, Lin JS, Mustafa RA, Horwitch CA, Wilt TJ; Clinical Guidelines Committee of the American College of Physicians. Screening for breast cancer in average-risk women: a guidance statement from the American College of Physicians. Ann Intern Med 2019;170:547-560.

Question: According to the American College of Physicians, how often should women at average risk be screened for breast cancer?

Bottom line: Citing that the harms of screening (false-positive results, benign biopsies, and overdiagnosis) outweigh the benefits of early diagnosis, the American College of Physicians (ACP) does not recommend routine screening of women between the ages of 40 years and 49 years; instead, the group suggests a discussion based on an overview of benefits and harms. Women aged 50 to 74 years should be offered screening every 2 years, stopping if they have a life expectancy of less than 10 years. Stop screening at age 75. If you haven't already, drop the clinical breast examination.

Design: Practice guideline; LOE: 5
Setting: Outpatient (any)
Synopsis: This statement starts with available guidelines that conflict with one another and scores them for validity using the AGREE II instrument, a guide for producing high-quality guidelines. The guideline development committee comprised members of the ACP and 2 public representatives without conflicts of interest (though why only one committee member is a women is a mystery to me). The resulting guidance was reviewed by the governance of the ACP. The committee scored several guidelines as low-quality based on methodology that did not have a formal means of linking benefits and harms with their recommendations or that based recommendations on observational or modeling studies to a greater extent than randomized controlled studies. Said by many but worth repeating: No studies have demonstrated a reduction in all-cause mortality with screening. Breast cancer–related mortality is reduced in women aged 50 to 69 years and 2 guidelines assert benefit for women 39 to 49 years of age. False-positive results leading to additional testing and unneeded treatment (overdiagnosis) are present in all groups, tempering benefit in women younger than 50. No studies have shown a benefit to clinical breast examination. (AS)