

Pros and Cons in General Medicine and Geriatrics, 2019

Domenico Cucinotta

Master in Geriatric Medicine, Ferrara and San Marino Universities; Past Chairman Dept of Internal Medicine and Aging, University Hospital, Bologna, Italy

The article takes into consideration a group of papers of 2019, focused on improving clinicians' abilities to treat adult and older patients, and looking at top stories physicians were talking about on media.

At the top of the list are guidelines saying that daily **low-dose aspirin** should be reserved for people with the highest cardiovascular risk and the lowest risk for bleeding. A useful meta-analysis showed that aspirin use for prevention did not reduce the risks for death, cardiovascular death, or fatal MI, while the benefits in risks for nonfatal MI and stroke seemed to be offset by bleeding risks. Estimates suggest that the risks outweigh the benefits for most primary prevention patients (1, 2). A meta-analysis offers clinicians more evidence on the benefits and harms of aspirin for the primary prevention of cardiovascular (CV) disease. Researchers examined 13 studies in which nearly 165.000 adults without CV disease were randomized to receive daily aspirin or no aspirin. Overall, during a median 5 years' follow-up, aspirin was associated with a lower risk for major CV events and a higher risk for major bleeding. The researchers estimated that 265 patients would need to be treated to prevent one CV event, and 210 to cause one bleeding event (3).

Not Quite Time for App-Detected **Atrial Fibrillation (AF)**. The Apple Watch has an optical sensor that can detect heart rates. The industry-sponsored, prospective, open-label, siteless, pragmatic Heart Study tested an algorithm to identify AF; it is groundbreaking because of its massive size and siteless method. However it has many limitations: large percentages of patients were lost to follow-up and the confirmation

method's sensitivity is unknown. Overall, the algorithm caught some AF episodes and missed others. At the moment we should not rely on the Apple Watch, but neither can we ignore this new opportunity. We certainly need more study about how to optimize such tools and, especially, how best to respond to brief, intermittent, subclinical AF episodes (4).

Ablating Atrial Fibrillation (AF) in Heart Failure Patients: AF frequently accompanies heart failure, particularly with reduced ejection fraction (HFrEF). A rhythm control strategy theoretically offers the potential for clinical benefit, but antiarrhythmic agents have not been proven to improve outcomes. Catheter ablation of AF might provide clinical benefit without the toxicities of antiarrhythmic agents but might involve procedural risks. The current researchers conducted a meta-analysis of six randomized, controlled trials, including CASTLE-AF, of AF ablation in patients with HFrEF. In the 775 patients, ablation compared with physician-directed medication (including rate-controlling agents or antiarrhythmic agents) was associated with lower rates of all-cause mortality (9.0% vs. 17.6%) and HF hospitalizations (16.4% vs. 27.6%). The two approaches had no significant differences in adverse events. AF ablation was also beneficial in improving left ventricular ejection fraction, 6-minute walk distances, and quality of life, and it could be extremely of benefit in older subjects.(5)

What the available data to tell us about how many older people are taking **statins** for primary prevention, and how much good is it likely doing them? The role of statin therapy in primary prevention of cardiovascular

disease in persons older than 75 years remains a subject of debate. An analysis of guideline-driven indications for statin use concludes that the drugs, especially when used for primary prevention in low-risk patients, may constitute low-value care. Researchers writing in *The BMJ* examined changes in eligibility for guideline-directed statin use between 1987 and 2016. They found that the proportion of people older than 50 in Ireland eligible for statin treatment rose from 8% to 61% over that period. As a result, the number needed to treat with statins to prevent one major cardiovascular event rose tenfold, from 40 to 400. Although there are clear benefits for high risk groups, the authors remind readers that statins' net benefits depend on the individual patient's baseline risks. For example, age, smoking status, and cholesterol status. With wide confidence intervals around measures of relative risk among patients at low baseline risk, the drug's effects also encompass the possibility of harm. This analysis should prompt physicians to think carefully about how they recommend statins for primary prevention (6). In spite of this, a nationwide study of 120,173 people in France, who were aged 75 between 2012 and 2014 and had been taking statins continuously for two years, has found those who stopped taking their statins had a 33% increased risk of being admitted to hospital with heart or blood vessel problems during an average follow-up period of 2.4 years. The study is the first to evaluate the impact of discontinuing statins taken for primary prevention in older people. The researchers stress that this is an observational, retrospective, non-randomised study and therefore cannot show that discontinuing statins can cause a heart attack or stroke, only that it is associated with it. Limitations of the study include the fact that statin use was defined by prescriptions dispensed, although the researchers point out that as the patients regularly had prescriptions dispensed to them, they would be unlikely not to take the medication; the researchers did not have information on patients' socio-economic status, their lifestyles, cholesterol levels at the start of the period being studied, tobacco use, obesity and frailty; and they did not have precise information on the reasons why people stopped taking statins (7).

Concerns regarding statin use and accelerated cognitive decline and/or memory loss keep surfacing

in mainstream media. These messages generated confusion as well as hurting statin adherence. But a recent paper concluded that the outcomes of the analysis of many researches were reassuring and confirmed earlier findings that refuted the suggested link between statin use and cognitive decline (8).

Another very important problem in older patients are Statin Associated Muscular Symptoms, with the increased risk of falling and reduction of gait speed and motility. It is up to the clinician to decide to stop or to continue statin, taking into consideration risk and benefits and willings of any patient.

Ultrasound Screening for Abdominal Aortic Aneurysms: The USPSTF reviewed the most recent evidence on screening for abdominal aortic aneurysms (AAAs; defined as aortic enlargement of ≥ 3.0 cm in diameter). One-time screening of older men (age range 65-75) who have ever smoked (at least 100 lifetime cigarettes) confers benefit of moderate certainty (B recommendation). Benefit of screening in older men who have never smoked is less clear and should be offered selectively, based on family history and risk factors such as history of other aneurysms, coronary or cerebrovascular disease, hyperlipidemia, and hypertension (C recommendation). Screening older women who have never smoked and have no family history of AAA likely will cause more harm than benefit (D recommendation). The Task Force found insufficient evidence to make a recommendation about screening older women who have ever smoked or who have family history of AAA. Maybe that these recommendations are influenced by the improved outcomes with endovascular repair that now is used preferentially over open repair. Optimal screening intervals for patients with aneurysms smaller than 5.5 cm in diameter are unknown (9-11).

Diabetes Groups Refine Recommendations for **Glucose-Lowering Drugs.** In certain high-risk people with diabetes, clinicians' decision to use a glucagon-like peptide 1 (GLP-1) receptor agonist or sodium-glucose cotransporter 2 (SGLT2) inhibitor to reduce cardiovascular and renal risk should be made without regard to baseline HbA1c or HbA1c target.

For patients with established atherosclerotic cardiovascular disease and diabetes for whom major adverse cardiovascular events are the largest threat, GLP-1 receptor agonists have the greatest benefit against CV events. This class can also be considered for patients with diabetes who don't have established CVD but are at high risk. For patients with heart failure with reduced ejection fraction or chronic kidney disease (CKD), SGLT2 inhibitors are the most beneficial option. For patients with diabetes and CKD, this class is recommended to prevent progression of CKD, heart failure hospitalization, major adverse cardiovascular events, and cardiovascular death. SGLT2 inhibitors are also recommended for people with foot ulcers and those at risk for foot amputation, but only after shared decision making about risks and benefits. In the "real world", SGLT2 use is associated with lower risks for heart failure, all-cause death, major adverse CV events, and CV-related death, findings that are consistent with those from randomized trials. Notably, the American Diabetes Association recommends an SGLT2 inhibitor or a glucagon-like peptide-1 receptor agonist as the first choice for a second-line agent in type 2 diabetics with CV disease, heart failure, or chronic kidney disease (12).

Acupuncture may help ease pain in patients with cancer? A meta-analysis compared acupuncture or acupressure with control therapies (placebo, sham acupuncture, analgesics, usual care) in over 900 cancer patients. Compared with sham acupuncture, real acupuncture was associated with reduced cancer pain intensity. Pain intensity was also lower for patients who received acupuncture or acupressure plus analgesics, relative to those who received only analgesics. Two studies found that patients assigned to acupuncture used lower analgesic doses than those who used only analgesics. We need more rigorous trials to identify the association of acupuncture and acupressure with specific types of cancer pain and to integrate such evidence into clinical care to reduce opioid use (13).

Measuring NT-ProBNP for Preoperative Cardiac Risk Assessment? Postoperatively, troponin T levels were measured daily (for as long as 3 days) to detect myocardial injury after noncardiac surgery

(MINS). Patients were stratified into four risk groups by preoperative NT-proBNP levels: <100, 100-199, 200-1499, and ≥ 1500 pg/mL. The overall incidence of MINS was 12%; most cases were asymptomatic elevations in troponin (and not clinical myocardial infarctions). In adjusted analyses, patients with increasingly higher NT-proBNP levels in the four risk groups had progressively – and significantly – higher incidences of MINS (5%, 12%, 21%, and 38%), vascular-related death (0.2%, 0.4%, 0.7%, and 2.9%), and all-cause mortality (0.3%, 0.7%, 1.4%, and 4.0%) within 30 days after surgery. In middle-aged or older adults (age, ≥ 45) who are scheduled for inpatient noncardiac surgery, adding NT-proBNP to the RCRI score could improve individualized preoperative risk stratification and could help patients decide whether potential risks associated with elective noncardiac surgery are acceptable. In theory, preoperative NT-proBNP levels also could help clinicians adjust preoperative investigations, guide surgical or anesthetic approaches, and more precisely intensify or lessen postoperative monitoring. However, whether additional diagnostic and therapeutic interventions triggered by routine perioperative measurement of NT-proBNP would lower postoperative morbidity and mortality is unclear (14).

Managing Dyspepsia with "Test and Treat" ranked best strategy (15). Five management strategies were compared: 1- Prompt endoscopy 2-Test for *H. pylori*, followed by endoscopy after positive findings 3-"Test and treat" (for the presence of *H. pylori*) 4-Empirical acid suppression 5- Symptom-based management. The approach resulting in the lowest risk of remaining symptomatic by the trials' final follow-up was "test and treat," with a relative risk of 0.89. That strategy just beat out prompt endoscopy (RR, 0.90). However, no strategy was clearly superior to any other. Prompt endoscopy gained the highest patient-satisfaction ratings; however, the authors point to the high costs involved with that approach. This is a very practical analysis of treatment modalities for a common problem in primary care. While no strategy was clearly superior, this study validates an inexpensive and commonly used approach by primary care clinicians that also will help patients avoid endoscopy. One of the most important findings of this study is the fact that upper gastrointestinal can-

cer rates were very low in all trials. This should give us comfort that each of these strategies is reasonable, with very little risk of adverse patient outcomes.

Over 40% of **Antibiotic Prescriptions** potentially inappropriate. Researchers studied antibiotic prescribing practices in a nationally representative sample of 28,000 ambulatory care visits from 2015. Among the other findings: roughly 25% of antibiotic prescriptions were inappropriate (e.g., for upper respiratory tract infection), and 18% lacked a documented indication. Primary care clinicians had lower rates of prescriptions without a documented indication (12%) than other specialists who often prescribe antibiotics (24%) or all other specialists (29%). When a culture was taken, clinicians were less likely to prescribe without an indication. Prescriptions for sulfonamides and urinary anti-infectives had higher rates of no documented indication than penicillins. Nearly one in five antibiotic prescriptions lacked documented indications. Some, if not many, of prescriptions might have been appropriate (e.g., a clinician reasonably might suspect a urinary tract infection and prescribe an anti-infective agent but code for a nonspecific symptom such as dysuria). Of course, inappropriate antibiotic prescribing should be avoided altogether (16).

Testosterone therapy can induce hematologic abnormalities associated with hypercoagulability, but whether it actually confers excess risk for venous thromboembolism (VTE) is controversial. When use of testosterone during the 6 months immediately preceding VTE (case period) was compared with use of testosterone during months 6 to 12 prior to VTE (the control period), testosterone therapy was associated significantly with development of VTE (odds ratio, ≈ 2.0). Outcomes were similar in patients with or without coded diagnoses of hypogonadism. Medical claims and pharmacy data have many potential sources of error, including inaccuracy in capturing all hypogonadism diagnoses. This study emphasizes the proximate nature of testosterone therapy and incident VTE, not necessarily the absolute risk for VTE with or without testosterone therapy (17). The American College of Physicians suggests that clinicians discuss whether to start testosterone therapy with men who have age-

related low testosterone and want to treat their sexual dysfunction, according to new guidelines published in the *Annals of Internal Medicine* (18). Testosterone is not recommended for other nonspecific symptoms of aging, like fatigue or cognitive decline. For men treated with testosterone, clinicians should schedule follow-up for 12 months later and occasionally thereafter. Treatment should be discontinued in men with no improvement in sexual function. Clinicians should consider intramuscular injection over transdermal application because of lower costs (18).

What is the best first-line treatment for patients with **hypertension**? According to current guidelines, based largely on randomized trials that are more than 2 decades old, thiazide or thiazide-like diuretics, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and calcium-channel blockers (CCBs) are acceptable first-line therapies. Researchers analyzed data from nine large observational databases from four countries (with data on 4.9 million patients with as long as 22 years of follow-up) and synthesized tens of thousands of between-drug comparisons in patients whose initial treatment was a single drug from any of the aforementioned classes (median patient follow-up, ≈ 2 years). Multiple advanced statistical techniques were applied to minimize confounding. ACE inhibitors were used most often for initial monotherapy (48% of patients), followed by thiazide or thiazide-like diuretics (17%), dihydropyridine calcium-channel blockers (e.g., amlodipine; 16%), angiotensin-receptor blockers (15%), and non-dihydropyridine calcium-channel blockers (e.g., diltiazem; 3%). Most comparisons showed no significant difference in incidence of the combined primary outcome (i.e., myocardial infarction, hospitalization for heart failure, and stroke) between classes, but thiazides conferred a significantly lower risk for all three outcomes relative to ACE inhibitors (hazard ratios, ≈ 0.8 for all outcomes), and non-dihydropyridine CCBs significantly underperformed all other classes. Compared with ACE inhibitors, thiazides were associated with significantly lower rates for 16 of 46 adverse safety outcomes. This massive data analysis, although retrospective, reveals real-world outcomes on a scale far beyond any conceivable randomized trial and sug-

gests that the most commonly prescribed drugs for initial antihypertensive treatment might not be the safest and most effective. In patients beginning hypertension monotherapy, diuretics are a more effective and safer option than angiotensin-converting enzyme (ACE) inhibitors. However, it's possible that patterns of effectiveness and adverse effects across drug classes would change with longer duration of follow-up (19). Clearly the choice of antihypertensive agent depends on multiple patient-related factors such as comorbidities. Nonetheless, it is reassuring to know that diuretics, which are inexpensive and well tolerated, can be safely used as first-line treatment for hypertension (19).

Acute gout and pseudogout usually are managed with colchicine, nonsteroidal anti-inflammatory drugs, steroids, or joint injections. However, in patients with comorbid conditions such as chronic kidney disease, heart failure, diabetes, or hypertension, these standard therapies often are avoided. The interleukin 1-receptor antagonist anakinra sometimes is used off-label in patients with acute crystal disease who cannot be managed with traditional therapy, although access is restricted because of its expense. In this retrospective observational U.S. study of 100 medically complex hospitalized patients (mean age, 60) with acute gout or pseudogout, researchers evaluated anakinra's efficacy and safety. Previous case reports of anakinra use for acute gout and pseudogout have been published, but this is the largest observational study in an inpatient setting; 75% of patients significantly improved within 4 days. No important adverse events occurred, even among these complex patients. This study, although retrospective and uncontrolled, offers support for anakinra treatment of acute crystal disease in patients with substantial comorbidities (20).

In older patients, **polypharmacy** (5 or more regular prescriptions) is associated with risks for falls, disability, and death, over and above risks associated with the illnesses the drugs are intended to treat. To examine the association between polypharmacy and falls in more detail, Canadian researchers prospectively evaluated gait patterns among 249 older adults (age ≥ 65) without gait-impairing neurological diagnoses. At baseline, the 176 patients who were taking more than

five medications (mean, 9 prescriptions), had more diagnosed illnesses, reported more falls in the previous year, and (on formal gait testing) walked considerably more slowly and haltingly than the other 73 patients. During 5 years of follow-up, gait parameters worsened more rapidly in the high-med group, even after controlling for age and comorbidity. The researchers calculated that every additional medication increased independent risk for gait deterioration by about 15% and increased fall risk by 5%. Most patients and caregivers agreed they would be willing to stop a medication on a physician's recommendation. Both clinicians and their older patients are to blame for those long lists of pills – physicians might prefer not to tamper with stable regimens, whereas patients often become oddly attached to familiar regimens. The goal: cutting back medications to the minimum is vital, especially in frail oldest persons (21).

Nutritional Recommendations implicate unprocessed red meat and processed meat in conferring adverse cardiovascular (CV) and cancer outcomes. However, all have one or more limitations: a) they include only observational studies, with high risk for confounding; b) they lack reporting of absolute magnitude of effects; c) they lack systematic review of the evidence; d) they omit authors' conflicts of interest; and e) they inconsistently incorporate population values and preferences. An independent panel addressed each of these limitations, using findings from five comprehensive meta-analyses. The panel's evaluation showed no significant difference between subjects who consumed higher versus lower quantities of red meat during longer than 10 years of follow-up for the outcomes of all-cause mortality, CV-related mortality, CV disease, or cancer-related mortality, including colorectal cancer (low- to very low-certainty evidence). The observational studies showed that, for every 100 people who reduced processed or unprocessed meat intake by 3 servings per week, roughly 1 person avoided death and 1 person avoided a diagnosis of diabetes during 11 years of follow-up. Adults may continue moderate consumption of unprocessed red meat and processed meat (weak recommendation, based on low-certainty evidence). Greater reductions in meat consumption than the "practical" 3 servings-per-week reductions

might yield greater reductions in adverse outcomes. The slightly better outcomes seen in the observational data require individuals to maintain relevant dietary changes over very long periods (>10 years) to gain benefit; very motivated individuals who maintain large reductions (>3 servings per week) in their very long-term meat intake might glean benefits. For people who are interested in reducing meat consumption (whether to improve health or mitigate the effects of meat production on the environment), certainly nothing argues against that lifestyle modification (22-24).

Too many PROS&CONS in 2019? Let's go to **conclusion:** Three Easy Ways to Save Almost 100 Million Lives Worldwide. Noncommunicable diseases (NCDs) are the leading cause of death worldwide and are largely preventable through changes in modifiable risk factors: increasing the coverage of hypertension treatment to 70%, reducing dietary sodium by 30%, and eliminating trans fats.(25) The three interventions could delay 94.3 million deaths during 25 years (39.4 million from boosting hypertension treatment, 40.0 million from reducing sodium intake, and 14.8 million from eliminating trans fats). The effects are greater for men than women and for older (age ≥ 70) than younger people. Three simple population-level interventions could dramatically decrease the global burden of NCDs. To achieve this goal, low- and middle-income countries in particular need public health resources and infrastructure to increase access to pharmacotherapy for hypertension, the leading modifiable risk factor for early cardiovascular disease. The interventions are not only feasible but extremely cost-effective. The lowest-hanging fruit might be eliminating trans fats through national legislation, as has been done in some high-income countries. What is clear from this and other similar analyses is that to substantially move the needle in cardiovascular disease prevention, interventions must move beyond the level of individual patients (25).

Conflict of interest: The author declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:

Domenico Cucinotta

Past Chairman

Dept of Internal Medicine and Aging,

University Hospital, Bologna

E-mail: cucin.d@libero.it