

Pros and Cons in General Medicine and Geriatrics - 2018

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A perspective on some research in the field of general medicine and geriatrics from the past year could give argument of discussion and should be used in common practice.

Many clinicians and family doctors were greatly pleased with a study discouraging use of digital rectal exams for routine prostate cancer screening, while others were greatly displeased by bacteria becoming tolerant to hospitals' alcohol handwashes.

The growth of the aging population leads to the increase of chronic diseases, of the burden of multimorbidity, and of the complexity polypharmacy. The prevalence of medication errors rises in patients with polypharmacy in primary care, and into residencies and hospitals too, and this is a major concern to healthcare systems.

The inappropriate use of medicines was pointed out in order to articulate recommendations on how to reduce it in chronic patients, particularly in the oldest, polymedicated and multipathological that take five or more medications a day.

Many papers demonstrated the importance of nutrition in general, and of physical activity, and their effects in aging process, and a lot of researchers discussed on the efficacy of calcium, vitamin D supplements, statins, and aspirin, focusing on prevention strategies, side effects and efficacy.

A prevention study demonstrated the value of 24-hour ambulatory **blood pressure monitoring** (ABPM). The clinical community has tended to use ABPM sparingly, but it predicted mortality more accurately than clinic measurement. Masked hypertension predicted mortality as strongly as sustained hypertension. In another meta-analysis, au-

tomated office blood pressure readings were more accurate than typical office readings among patients with hypertension (*JAMA Internal Medicine*). Researchers examined 31 studies of 9300 people that compared fully automated office BP readings, in which a clinician was not present and the patient was resting quietly, to other methods of BP measurement. Among patients with automated systolic BP of 130 mm Hg or higher, systolic BP readings taken at routine office visits were significantly higher than automated readings (mean difference, 14.5 mm Hg). Meanwhile, automated BP readings and awake ambulatory BP readings were statistically similar. The usefulness of light technology should strongly influence incoming epidemiological studies in hypertension.

Liquid biopsy (LB) is a blood test that can spot early-stage cancers by identifying circulating tumor cells (CTC) or cell-free DNA from tumors that has been shed into the blood. This technology could accurately detect the methylation pattern of very small amounts of circulating tumor DNA. Seven different malignancies (lung, breast etc) were tested, and each had a characteristic methylation pattern. The accuracy of the test was very high (very few false negatives or false positives), even in patients with early-stage cancers. The performance of this inexpensive blood test to detect early-stage cancers is encouraging, also if whether the test has value in patients with cancer who are presymptomatic remains to be determined. LB could help diagnose and monitor cancer, and tracking circulating tumor cells in metastatic patients could prove effective in this application and treatment planning. Identifying and characterising CTC in cancer

patients should provide a unique insight into metastatic disease, which is responsible for over 90% of cancer deaths. CTC detection could also help unravel new therapeutic targets for cancer treatment. (Shen SY et al. *Sensitive tumour detection and classification using plasma cell-free DNA methylomes. Nature* 2018 Nov 22; 563:579).

Personalised Physical Exercise for in-hospital prevention. An individualised, multicomponent exercise program proved safe and effective to reverse the functional decline associated with acute hospitalisation in oldest patients (*JAMA Internal Medicine*). The in-hospital intervention included individualised moderate-intensity resistance, balance, and walking exercises (2 daily sessions). The primary endpoint was change in functional capacity from baseline to hospital discharge, assessed with the Barthel Index of independence and the Short Physical Performance Battery (SPPB). Secondary endpoints were changes in cognitive and mood status, quality of life, handgrip strength, incident delirium, length of stay, falls, transfer after discharge, readmission rate, and mortality at 3 months after discharge. The exercise intervention program provided significant benefits over usual care, and also improved the SPPB score and benefits were also found at the cognitive level. Intervention involving innovative, personalised multicomponent physical exercise that includes moderate intensity endurance training over a very short period of time has a significant benefit on routine care, and may help to reverse the functional and cognitive deterioration associated with the hospitalisation of old patients, fighting the risk of bedrest and immobility.

Exercise training is associated with lower risk for falls and possibly for fall-related injuries. In a meta-analysis of 40 randomized, controlled trials (mean duration, 17 months) that involved almost 22,000 community-dwelling or institutionalized old persons (mean age 73 yrs), researchers explored the value of exercise in lowering risk for falls, fractures, hospitalizations, and death. Researchers found no beneficial effects on hospitalization or death among participants in exercise programs compared with those in control groups. In trials for which fracture rate was reported as

an outcome, fewer fractures occurred among those who exercised, but the difference was not statistically significant. In trials for which fall and injurious fall rates were reported, 12% fewer falls and 26% fewer injurious falls occurred in exercise programs (de Souto Barreto P et al. *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* 2018 Dec 28; [e-pub]). Another important study demonstrated that life expectancy increases as **aerobic fitness** improves with no upper limit of benefit at any age (Mandsager K et al, *association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing JAMA* 2018). Cleveland Clinic researchers are reassuring that, with regards to mortality, one can exercise safely at an elite level throughout life. But those who aren't interested in achieving elite levels still will derive mortality benefits when they improve their cardiorespiratory fitness.

Moving More in Old Age May Be Linked to Sharper Memory: older adults who move more, either with daily exercise or simple routine physical activity like housework, may preserve more of their memory and thinking skills, even if they have brain lesions or biomarkers linked to dementia. Exercise is an inexpensive way to improve health, and perhaps it may have a protective effect on the brain. But it is important to note that this study does not show cause and effect. It may also be possible that as people lose memory and thinking skills, they reduce their physical activity. More studies are needed to determine if moving more is truly beneficial to the brain. (*American Academy of Neurology* 2018).

Frailty and sarcopenia have emerged as serious public health concerns worldwide and major reasons for the loss of functional independence among older people. An easier way to screen for sarcopenia risk using simple questionnaires, a systematic way to make the diagnosis, and suggestions for practical tools and tests at each step are needed. The consensus also underscores the importance of poor physical function as a "red flag" for severe sarcopenia. There are multiple types of sarcopenia, driven by different underlying risk factors or diseases, An important step is classify-

ing the syndrome into primary and secondary forms to make the pathophysiological diagnosis and care. Eating more protein could contribute to fighting sarcopenia and frailty, helping people maintain independence as they grow older (*Journal of the American Geriatrics Society*). Protein is known to slow the loss of muscle mass and having enough muscle mass can help preserve the ability to perform daily activities and prevent disability. Older adults tend to have a lower protein intake than younger adults due to poorer health, reduced physical activity, and changes in the mouth and teeth. Older who ate more protein were less likely to become disabled when compared with those who ate less protein.

Vitamin D deficiency is common in older people, and it may lead to bone loss, impairment of muscle function, and frailty. The results from studies assessing the effect of vitamin D on bone mineral density have yielded conflicting results. Vitamin D supplementation doesn't seem to prevent fractures or falls, according to a large meta-analysis. Researchers analyzed 81 randomized trials that compared vitamin D supplementation (with or without calcium) to placebo, control, or lower-dose vitamin D among 54,000 adults. Vitamin D supplementation had no significant effect on fractures, hip fractures specifically, or falls. Supplementation's effects on bone mineral density were inconsistent and not clinically meaningful. The authors conclude: "There is little justification for the use of vitamin D supplements to maintain or improve musculoskeletal health, and clinical guidelines should reflect these findings. The clear exception to this is for the prevention or treatment of the rare conditions of rickets and osteomalacia" (*Lancet Diabetes & Endocrinology*). Further analysis is underway on the effects of sun exposure on vitamin D levels in older people and the impact of vitamin D supplements on muscle strength. Experts are also looking at the impact of genes and kidney function on vitamin D levels and their function in the blood, but enthusiasm for recommending vitamin D supplementation to prevent a wide range of skeletal and extraskel-etal disorders was diminished considerably.

Does Cardiovascular Health Influence Risk for Dementia? In a study in older adults (mean age, 74 yrs)

without CV disease or dementia subjects were assessed at baseline for optimal measures of CV health, smoking status, physical activity, diet, body-mass index, cholesterol level, blood pressure, and fasting glucose level. After mean follow-up of 8.5 years, dementia incidence, as assessed by structured instruments and physician assessments, was associated inversely with number of optimal CV risk factors at baseline. For example, the incidence of dementia in people with less than 2 factors at optimal levels was 1.56/100 person-years, compared with 0.83 for people who had 5 to 7 optimal factors. Controlling for demographic, clinical, and socioeconomic variables yielded similar results. Also, studies in young adults support promoting CV health to lower dementia risk in older adults. (*Samieri C et al. Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA 2018 Aug 21; 320:657; Williamson W et al. Association of cardiovascular risk factors with MRI indices of cerebrovascular structure and function and white matter hyperintensities in young adults. JAMA 2018 Aug 21; 320:665; Saver JL and Cushman M. Striving for ideal cardiovascular and brain health: It is never too early or too late. JAMA 2018 Aug 21; 320:645*).

Mild Hypertension treatment, in low-risk patients, might not reduce mortality and could induce side effects. The American College of Cardiology and American Heart Association currently recommend that all patients with systolic blood pressure at or above 140 mm Hg or diastolic BP at or above 90 mm Hg receive antihypertensive therapy. Using U.K. electronic medical records, researchers matched 19,000 adults with mild hypertension (140/90-159/99 mmHg) and low cardiovascular risk who received antihypertensive medication to another 19,000 who weren't treated. During a median 6 years' follow-up, rates of mortality and cardiovascular disease were similar between the groups. Antihypertensive treatment was, however, associated with higher risk for hypotension, syncope, electrolyte abnormalities, and acute kidney injury (*JAMA Internal Medicine*).

Aspirin for Primary Prevention of CV Disease? The role of aspirin in the primary prevention setting is continuously evolving. Recent randomized trials have challenged the role of aspirin in the primary preven-

tion setting. Electronic databases were searched for randomized trials that compared aspirin vs. placebo (or control) in subjects without established atherosclerotic disease. The primary efficacy outcome was all-cause mortality, while the primary safety outcome was major bleeding. At a mean follow-up of 6.6 years, aspirin was not associated with a lower incidence of all-cause mortality [risk ratio (RR) 0.98, 95% confidence interval (CI) 0.93-1.02; $P=0.30$]; however, aspirin was associated with an increased incidence of major bleeding (RR 1.47, 95% CI 1.31-1.65; $P<0.0001$) and intracranial haemorrhage (RR 1.33, 95% CI 1.13-1.58; $P=0.001$). A similar effect on all-cause mortality and major bleeding was demonstrated in diabetic and high cardiovascular risk patients (10-year risk more than 7.5%). Aspirin was associated with a lower incidence of myocardial infarction (RR 0.82, 95% CI 0.71-0.94; $P=0.006$); however, this outcome was characterized by considerable heterogeneity, and sequential analysis confirmed the lack of benefit of aspirin for all-cause mortality up to a relative risk reduction of 5%. In conclusion, among adults without established cardiovascular disease, aspirin was not associated with a reduction in the incidence of all-cause mortality; however, it was associated with an increased incidence of major bleeding. The routine use of aspirin for primary prevention needs to be reconsidered. (*European Heart Journal*).

Fluoroquinolone antibiotics are associated with increased risk for aortic dissection and aneurysm. The caution applies to all systemic fluoroquinolones. The FDA said that while there are limitations to the data, the evidence appears to be consistent across multiple epidemiological studies showing an approximately two-fold increased risk over the baseline risk of aortic aneurysm or dissection in each study. The FDA offers the following advice for clinicians: a) do not prescribe fluoroquinolones to patients with, or at risk for, an aortic aneurysm, unless there are no other options. Such patients include older adults and those with peripheral atherosclerotic vascular disease, hypertension, Marfan syndrome, and Ehlers-Danlos syndrome; b) tell all patients to seek immediate medical attention if they develop symptoms of aortic aneurysm, c) stop fluoroquinolones right away if patients have symptoms of aortic aneurysm or dissection.

Statins for primary prevention in elders? With few studies and objective data for prescribing statins in the very old, this remains today an important question. Guidance on appropriate use of statins for primary prevention of cardiovascular disease has become increasingly confusing. Some study suggests that we are overtreating. Guidelines on cardiovascular disease (CVD) prevention classify most elders as eligible for statin therapy, because CVD risk is highly associated with age. However, little evidence supports statins for primary prevention in these patients. In a recent retrospective study, statins did not lower risks for atherosclerotic CVD and all-cause death among participants without diabetes. The guideline-recommended risk thresholds for initiating statins for primary prevention of cardiovascular disease may be too low, and have to be balanced with potential harms, like myopathy, hepatic or renal dysfunction, cataracts, hemorrhagic stroke, type 2 diabetes, and cancer. Most current guidelines recommend statin initiation when a person's 10-year CVD risk is 7.5%-10%, but in recent studies the benefits only began to outweigh the risks when CVD risk was 21% for men of 70 to 75 years; for women, thresholds ranged from 17% to 22%. The lipid management of old patients is not an easy challenge. On the one hand, simply because of age the risk is high, and statins would be effective in reducing this risk, but we have to consider the potential harms related to drug-drug interactions, secondary disease/pathology, competing for risk of deaths, life expectancy and preference of patients as well. Weighing the pro's and con's, including the co-morbidities and co-medications is pivotal with a strong emphasis on well informed shared decision making, particularly in frail aged people (*Ramos R et al. BMJ 2018 Sep 5 ; Yandrapalli S, Gupta S, Andries G et al. Drug Therapy of Dyslipidemia in the Elderly. Drugs Aging 2019*).

Omega-3 Polyunsaturated Fatty Acid: are they associated with Healthy Aging? Although consuming long-chain ω -3 polyunsaturated fatty acids (PUFAs) has favorable physiological effects (on endothelial function), the relation between plasma PUFAs and healthy aging has not been established. In a prospective cohort study, researchers determined the longitudinal association between serial measures of summed

and individual plasma PUFAs and α -linolenic acid and healthy aging into 2622 persons (mean age 74 yrs) with healthy aging at baseline, defined as absence of cardiovascular disease, cancer, lung disease, severe chronic kidney disease, and cognitive and physical dysfunction. During the study, 89% of participants experienced unhealthy aging. In an analysis that was adjusted for multiple variables, risk for unhealthy aging was 18% lower in participants in the highest PUFA quintile compared with those in the lowest PUFA quintile. A significant dose-response trend was observed. Assessed individually, higher intake of eicosapentaenoic and docosapentaenoic acid was associated with lower risk for unhealthy aging. Higher plasma levels of PUFAs, especially seafood-derived eicosapentaenoic acid and endogenous and seafood-derived docosapentaenoic acid, were associated with higher likelihood of healthy aging. However, given the study design, causality could not be established, residual confounding was possible, and the results might not be generalizable to younger people. Nonetheless, the results support for increased consumption of fish (*Lai HTM et al. Serial circulating omega 3 polyunsaturated fatty acids and healthy ageing among older adults in the Cardiovascular Health Study: Prospective cohort study. BMJ 2018 Oct 17;363:k4067; Zhu Y et al. Omega 3 polyunsaturated fatty acids and healthy ageing: Fresh evidence provides clues to healthier, not just longer lives. BMJ 2018 Oct 17; 363:k4263*). Another meta-analysis of 10 randomized trials (78,000 total patients) showed no significant differences between ω -3 recipients and controls in risks for coronary heart disease-related death, nonfatal MI, any coronary heart disease event, or major adverse CV events overall. Subgroup analyses among participants with known coronary heart disease or diabetes yielded similar findings (*JAMA Cardiol 2018; 3:225*). Many trials do not support the use of ω -3 fatty acid supplements for preventing adverse CV events in patients with no history of CV disease. Work in progress!

Diabetes Guidelines Updated. The document (*Diabetes Care*) includes all of the group's current clinical practice recommendations related to diabetes treatment and care. Among the recommendations: a) for patients with type 2 diabetes who require an injectable drug, a glucagon-like peptide 1 receptor agonist is pre-

ferred over insulin, b) for patients with type 2 diabetes who aren't using insulin, routine glucose self-monitoring is of limited additional benefit, c) ten-year atherosclerotic cardiovascular disease risk should be part of a patient's overall risk assessment, d) water intake should be stressed, and consumption of sugar-sweetened and nonnutritive-sweetened beverages should be discouraged. The proliferation of pharmacologic agents available for glycemic control in diabetes has made the therapy of diabetes much more complicated, thus having evidence-based guidance is quite useful.

Is Glycemic Management Too Intensive in Older Diabetic Patients? Too many older diabetic patients are being managed intensively with medications that confer high risk for hypoglycemia. Many clinicians are unaware of guidelines that advise less-intensive glycemic targets in this population. More specific directives on de-escalating drug treatment and minimizing risk for hypoglycemia in older patients, in particular in frail or dependent subjects must be widespread. Tight glycemic control is unlikely to benefit older people with longstanding type 2 diabetes and is associated with excess risk for hypoglycemia (*Arnold SV et al. J Am Geriatr Soc 2018 Apr 10*). SGLT2 Inhibitors Are Associated with Risks for Amputation and Diabetic Ketoacidosis. In randomized trials, patients with type 2 diabetes and elevated cardiovascular disease (CVD) risk who received canagliflozin experienced fewer adverse CV events but more lower-limb amputations than did placebo recipients (*NEJM JW Gen Med Aug 1 2017 and N Engl J Med 2018; 377:644*). In a new cohort study, SGLT2 inhibitors were associated with significantly higher risks for lower-limb amputation (hazard ratio, 2.3) and diabetic ketoacidosis (DKA; HR, 2.1) but not bone fracture, acute kidney injury, serious urinary tract infection, venous thromboembolism, or acute pancreatitis. Although canagliflozin already carries an FDA black-box warning about amputation risk, the American College of Cardiology recently recommended SGLT2 inhibitors (and GLP-1 receptor agonists) to lower CVD risk in patients with type 2 diabetes and established CVD (*J Am Coll Cardiol 2018 Nov 26; [e-pub]*). **What to do?** The authors speculate that volume depletion induced by SGLT2 inhibitors might be a mechanism by which they confer

risks for amputation and DKA. Clinicians might want to avoid prescribing SGLT2 inhibitors to patients who are prone to volume depletion and those with known lower-extremity peripheral vascular disease (*Ueda P et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: Nationwide register based cohort study. BMJ 2018 Nov 14; 363:k4365*). **A hard commitment?**

A good new: middle aged adults with five low-risk lifestyle factors (healthy diet, never smoking, moderate to-vigorous physical activity, moderate alcohol consumption and healthy body mass index) could live more than a decade longer than their less healthy peers (*Circulation 2018*). The research found that each low-risk factor was associated with signifi-

cantly reduced risk for all cause, and for cardiovascular mortality: 74% for those who met all five criteria average life expectancy at age 50 was extended of 14 years longer for women and 12 years longer for men with all five low-risk factors.

Conflict of interest: None to declare

Received: 7 January 2019

Accepted: 7 February 2019

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