2021- Pros and Cons in General Internal Medicine and Geriatrics

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2021-What was the state of opportunities and challenges of care in older adults?: Multimorbidity and frailty have emerged as the greatest challenges in general medicine and geriatrics facing health services, both presently, in SARS-Cov-2 pandemic, and in coming years. Old population is projected to have four or more chronic conditions with a huge heterogeneity sometimes with abuse of many specialists consultation, and interlinked nature of physical and mental health conditions, with functional decline and loss of independency (1). Prevention and treatment services should reflect the population driving the demand, and proactively future proof the health system for impending demands. This approach would require a shift from a single disease focus to a person-centred approach, so that comorbidity gains match that of longevity. In this context recognizing frailty is extremely important, as a condition of increased vulnerability to endogenous and exogenous stressors, leading to decreased functional reserve capacities. The effect of frailty on old patient's clinical outcomes has been examined in several settings of care, and today also in old patients with COVID-19 infection, to guide their triage and treatment (2).

We recently got two oral treatments for outpatients with COVID-19: both agents are clinicaly effective, but uncertainties still attend their use. Immune modulators tocilizumab and baricitinib are recommended only for selected severely ill patients, whereas frailty is the rule in oldest oupatients with Covid 19. Three monoclonal antibody therapies have received approval in some countries for use in patients at high risk for progression to severe illness. But great benefit comes from vaccines and administering the third dose (booster), in Israel decreased infection rates 10-fold and mortality by about 90%. Robust SARS-Cov-2 specific memory B cell and T cell responses induced by mRNA vaccines are present after initial antibody levels wane. Moreover, subjects who develop COVID-19 despite being fully vaccinated are considerably less infectious for contact persons, who in turn are protected from infection if vaccinated.

Let's give a look at some researches carried out independently of COVID-19 pandemia:

Prediabetes: Not a Strong Predictor of Diabetes in Older Adults (3): The researchers compared different prediabetes definitions and characterize the risks of prediabetes and diabetes among older adults in a community-based setting (3,400 older adults, aged 71-90 years). Prediabetes prevalence varied greatly depending on definitions: 44% used HbA_{1c} level (5.7%–6.4%), 59% impaired fasting plasma glucose (IFG: according to ADA criteria:100–125 mg/dL) or both. During the 6.5-year follow-up period, there were 156 incident total diabetes cases (118 diagnosed) and 434 deaths. Using the HbA_{1c} for definition of prediabetes, 9% progressed to diabetes, 13% regressed to normoglycemia and 59% remained stable. Using IFG according to ADA criteria, 8% progressed to diabetes, while 44% regressed to normoglycemia, and 32% did not present significant changes. These findings suggest that prediabetes may not be a robust diagnostic entity in older age. In conclusion, pre-diabetes is a risk state,

not a disease, and is only of relevance to patients that fulfil certain criteria. Therefore, according to Burch and Holm, "a pragmatic ethical approach can be used to guide a clinician when deciding how to manage an unexpected prediabetic blood result in an elderly patient" (4).

Treated Diastolic Blood Pressure: How Low Is Too Low? (5): Current U.S. guidelines recommend a systolic blood pressure (SBP) target below130 mm Hg but don't specify the lower DBP limit. However, it has been postulated that pharmacological treatment to achieve a lower SBP target in persons whose DBP is already low may worsen patient outcomes. Researchers conducted a post hoc analysis of data from some 7,500 adult participants of recent blood pressure intervention trials (SPRINT and ACCORD-BP) who achieved a treated SBP < 130 mm Hg. Patients treated with a DBP level <60 mm Hg had significantly increased risks for adverse cardiovascular (CV) events compared to those with a DBP of 70 - < 80 mm Hg. This article provides some guidance for a situation encountered almost daily in a primary care office, that demonstrates the potential risk of overtreatment of a medical condition, in this case hypertension , and gives a practical guidance for the lower limits of DBP control.

Should blood pressure be lowered in all patients at high risk for adverse cardiac events? (6): The aim of authors was to investigate whether the benefits of blood pressure-lowering drugs are proportional to baseline cardiovascular risk. The meta-analysis showed that a 5 mm Hg reduction of systolic blood pressure (SBP) reduced the risk of major cardiovascular events by about 10%, irrespective of previous diagnoses of cardiovascular disease, and even at normal or high–normal blood pressure values. These findings suggest that a fixed degree of pharmacological blood pressure lowering is similarly effective for primary and secondary prevention of major cardiovascular disease, even at blood pressure levels currently not considered for treatment. Physicians communicating the indication for blood pressure lowering treatment to their patients should emphasise its importance on reducing cardiovascular risk rather than focusing on blood pressure reduction itself.

Comparative effectiveness of aspirin dosing in cardiovascular disease (7): The appropriate dose of aspirin to lower the risk of death, myocardial infarction, and stroke and to minimize major bleeding in patients with established atherosclerotic cardiovascular disease is a subject of controversy (8). Using an open-label, pragmatic design, patients with established atherosclerotic cardiovascular disease were randomly assigned to a strategy of 81 mg or 325 mg of aspirin per day. The primary effectiveness outcome was a composite of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke, assessed in a time-to-event analysis. The primary safety outcome was hospitalization for major bleeding, also assessed in a time-to-event analysis. A total of 15,076 patients were followed for a median of 26.2 months. Hospitalization for major bleeding occurred in 53 patients (estimated percentage, 0.63%) in the 81 mg group and 44 patients (0.60%) in the 325 mg group. Patients assigned to 325 mg had a higher incidence of dose switching than those assigned to 81 mg (41.6% vs. 7.1%) and fewer median days of exposure to the assigned dose (434 days vs. 650 days). In conclusion there were no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg daily dose of aspirin.

Low dose aspirin and cancer in older adults: aspirin increased cancer-specific mortality in people older than 70 yrs (8): The authors previously reported that among older adults taking low dose aspirin for primary prevention in the ASPREE RCT (ASPirin in Reducing Events in the Elderly- Randomized Controlled Trial), there was an increased mortality rate, largely attributed to a higher death rate from cancer. A randomized, double-blind, placebo-controlled trial of daily low-dose aspirin (100 mg) in older adults, showed an increase in all-cause mortality, primarily due to cancer. In contrast, prior randomized controlled trials, mainly involving younger individuals, demonstrated a delayed cancer benefit with aspirin. In this trial 19,114 community-dwelling participants aged 70 years and older without cardiovascular disease, dementia, or physical disability were randomly assigned and followed for a median of 4.7 years. Fatal and nonfa-

tal cancer events, a prespecified secondary endpoint, were adjudicated based on clinical records. 981 cancer events occurred in the aspirin and 952 in the placebo groups. There was no statistically significant difference between groups for all incident cancers but in older adults participating to the study, aspirin treatment had an adverse effect on later stages of cancer evolution. In summary, these findings suggest that "in older persons, aspirin may accelerate the progression of cancer and, thus, suggest caution with its use in healthy adults predominantly 70 years of age or older.

Association of Non-Steroidal Anti-Inflammatory Drugs with Kidney Health in Ambulatory Older Adults (9): Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, especially in older adults, however, their use is limited by potential adverse effects including cardiovascular toxicity, peptic ulcers, and nephrotoxicity.To exclude that the use of NSAID could be be associated with kidney damage and dysfunction, the authors compared baseline kidney function and kidney tubule biomarkers among NSAID users and non-users and evaluated the association of NSAID use with longitudinal estimated glomerular filtration rate (eGFR) changes. Surprisingly, the study didn't show an association between use of NSAIDs and decline in renal function in subjects with a mean age of 74 years (51% were females). No eGFR differences were detected between NSAID users (n = 655) and non-users (n = 2,344) at baseline (72 ml/min/1.73 m^2 in both groups). No significant differences in baseline concentrations of the remaining urine biomarkers were detected. Nevertheless, more research is needed to define safe patterns of NSAID consumption, considering the large use of these drugs in the real world and the potential for other NSAID-related adverse events in older adults, including GI bleeding, atherosclerotic events and heart failure.

What is the association between risk-enhancing factors and incident atherosclerotic cardiovascular disease (AASCVD) by coronary artery calcium (CAC) burden among intermediate-risk individuals? (10): The 2018 American Heart Association/American College of Cardiology Guidelineon the Management of Blood Cholesterol recommends the use of risk-enhancing factor assessment and the selective use of coronary artery calcium (CAC) scoring to guide the allocation of statin therapy among individuals with an intermediate risk of atherosclerotic cardiovascular disease (ASCVD). In a cross-sectional study, among participants with CAC scores of 0, the presence of risk-enhancing factors was generally not associated with an overall ASCVD risk that was higher than the recommended treatment threshold for the initiation of statin therapy. The use of CAC scoring was associated with significant improvements in the reclassification and discrimination of incident ASCVD. The results support the utility of CAC scoring as an adjunct to risk-enhancing factor assessment to classify individuals more accurately with an intermediate risk of ASCVD who might benefit from statin therapy.

Is revascularisation warranted for patients with Intermittent Claudication? (11): The mainstay of treatment for patients with peripheral arterial disease and intermittent claudication is exercise, smoking cessation, and management of vascular risk factors. Invasive treatment (percutaneous or surgical revascularization) is warranted for limb-threatening ischemia, but its role in patients with stable claudication is unclear. In a single-site retrospective study of 1,051 patients with intermittent claudication researchers compared outcomes for medically managed patients (69%) and revascularized patients (31%). Patients who underwent revascularization for limb-threatening ischemia were excluded. In analyses adjusted for confounding variables, eventual development of chronic limb-threatening ischemia was significantly more common in revascularized than in medically managed patients. In a propensity-matched comparison between revascularized and medically managed patients, absolute 5-year risks for progression to chronic limb-threatening ischemia were 18% and 8%, respectively; risks for ipsilateral amputation were 6% and 1%, respectively. The finding that invasive intervention is associated with worse long-term outcomes is concerning, especially given recent documentation that vascular interventions are overused in patients with newly diagnosed claudication. In a recent randomized trial, revascularization plus medical management was associated with early improvement in quality of life (compared with

medical management alone), but that benefit was lost over several years. In conclusion invasive treatment should be reserved for patients who have failed medical management and truly have significant lifestyle-limiting claudication symptoms.

Controversial FDA Approval of Alzheimer's Drug Aducanumab (12): Amid significant controversy, the FDA recently approved the drug aducanumab for the treatment of Alzheimer's disease (AD). The FDA stated that there was "evidence that AD reduces amyloid beta plaques in the brain" and that this "is reasonably likely to predict important benefits to patients". However, the FDA approved AD conditionally, requiring running a confirmatory trial to demonstrate clinical benefit. In theory, if the confirmatory trial doesn't show benefit, the FDA could withdraw its approval. According to the US FDA prescribing information, treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of the progressive neurodegenerative ailment. How does AD work? Amyloid is a protein that clumps in the brain (plaques) and may cause Alzheimer's disease. AD is a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid β The central controversy is whether the amyloid clearance protects patients from cognitive and functional decline. The clinical trials of AD studied a limited, specific group of patients. The most common side effects of AD include areas of brain swelling, small brain bleeding, headache, or falls. The areas of brain swelling, and small brain bleeding are usually temporary and resolve over time. Everyone who receives AD should have periodic MRIs to monitor for brain damage either with other side effects like headache, confusion, dizziness, vision changes, and nausea. Right now, the cost to patients is unknown, but we can expect that it will very high.

Can Sildenafil Cut Risk of Alzheimer's Disease? (13): Currently, there's no cure for Alzheimer's disease. (AD), but a recent study has found that people who took sildenafil were 69% less likely to develop AD over 6 years than those who did not take the drug. To understand how sildenafil might affect AD, the researchers grew neurons from stem cells derived from AD patients. In the model, they found that sildenafil increased brain cell growth and decreased hyperphosphorylation of tau proteins (a hallmark which leads to neurofibrillary tangles), offering biological insights into how sildenafil may influence disease-related brain changes. Taken together, these results show an association between sildenafil use and reduced AD risk. Would it be the cure of these patients a single drug? The mission is quite impossible. More studies are needed to verify the results, hoping serendipity could be of help to cure dementia in the future, taking into consideration that pure AD is rare, whereas the greatest group of demented are old and very old persons where multiple factors are of pathogenetical importance.

Bone mineral density: decreases less than expected at the femoral neck in postmenopausal women, by an average of 10% during a 25-year follow-up, according to a new study (14). Being the world's hitherto longest follow-up of changes in bone mineral density in postmenopausal women, the study shows that bone loss after menopause is significantly lower than has previously been assumed based on earlier studies. Women with the highest bone mineral density at baseline had the highest bone loss percentage. There were also surprisingly few risk factors affecting bone mineral density. The most significant factor protecting against bone loss was hormone replacement therapy as well as weight gain during the follow-up. This new, long-term follow-up of bone mineral density sheds significant new light on osteoporosis and bone research, and changes our understanding of bone loss in older women.

What's coming in near future? The development of Artificial Intelligence (AI) is advancing rapidly and its use in diagnosis and therapy is growing, in analysis for oncological problems, for gastrointestinal diseases, etc. A group of scientists (15) suggests that by tracking eye movement behavior with MRI and AI they can gave an insight into a number of neurological disorders and can support the diagnosis in many cognitive or neural syndrome. The AI technology is exciting and its use in clinical practice could give origin to a new era in healthcare of patients of all ages, who will ultimately benefit.

References

1. The healthy ageing conference recordings, London, 15-16 November,2021
2. Bellelli G, Rebora P, Valsecchi MG, Bonfanti P, Citerio G; COVID-19 Monza Team members. Frailty index predicts poor outcome in COVID-19 patients. Intensive Care Med. 2020;46:1634-6.
3. Rooney MR, Rawlings AM, Pankow JS, Echouffo Tcheugui JB, Coresh J, Sharrett AR, et al. Risk of Progression to Diabetes Among Older Adults With Prediabetes. JAMA Intern Med 2021;181:511-19.
4. Burch P, Holm S. Pre-diabetes in the elderly and the seesaw model of paternalism J Med Ethics 2021;47:719–21.
5. Hartsell SE, Beddhu S. Diastolic Blood Pressure and the J-Curve-Causal Effect or Confounding? JAMA Netw Open 2021;4(10):e2130031.
6. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014 ;384:591-58.
7. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med 2018;379:215-225.
8. McNeil JJ, Gibbs P, Orchard SG, Lockery JE, Bernstein WB, Cao Y, et al; ASPREE Investigator Group. Effect of Aspirin on Cancer Incidence and Mortality in Older Adults. J Natl Cancer Inst 2021;113:258-65.
9. Amatruda JG, Katz R, Peralta CA, Estrella MM, Sarathy H, Fried LF, et al.; Health ABC Study. Association of Non-Steroidal Anti-Inflammatory Drugs with Kidney Health in Ambulatory Older Adults. J Am Geriatr Soc 2021 ;69:726-34.
10. Patel J, Pallazola VA, Dudum R, Greenland P, McEvoy JW, Blumenthal RS, et al. Assessment of Coronary Artery Calcium Scoring to Guide Statin Therapy Allocation According to Risk-Enhancing Factors: The Multi-Ethnic Study of Atherosclerosis. JAMA Cardiol 2021; 6:1161-70.
11. Madabhushi V, Davenport D, Jones S, Khoudoud SA, Orr N, Minion D, et al. Revascularization of intermittent claudicants leads to more chronic limb-threatening ischemia and higher amputation rates. J Vasc Surg 2021;74:771-9.
12. Rabinovici GD. Controversy and Progress in Alzheimer's Disease - FDA Approval of Aducanumab. N Engl J Med 2021;385:771-4.
13. Fang J, Zhang P, Zhou Y, Chiang CV,Tan J, Hou Y, et al. Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease Nat. Aging 2021 Dec 6. doi: 10.1038/s43587-021-00138-z.
14. Moilanen A, Kopra J, Kröger H, Sund R, Rikkonen T, Sirola J. Characteristics of Long-Term Femoral Neck Bone Loss in Postmenopausal Women: A 25-Year Follow-Up. J Bone Miner Res 2021. doi: 10.1002/jbmr.4444.
15. Frey M, Nau M, Doeller CF. Magnetic resonance-based eye tracking using deep neural networks. Nat Neurosci 2021;24:1772-19.

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