Geriatrics Research Review™

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Issue 19 - 2022

In this issue:

Abbreviations used in this issue:

ACE = angiotensin-converting enzyme; **CFS** = Clinical Frailty Scale; **CI** = confidence interval; **HR** = hazard ratio.

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Welcome to the latest issue of Geriatrics Research Review.

Geriatric palliative oncology care can be optimised by including geriatric assessment-guided recommendations according to results from the GAP70+ trial published in *The Lancet* that show a significant reduction in the burden of serious toxic events as well as a reduction in falls. Multidisciplinary collaboration may be required to implement this in practice but the benefits certainly seem to be substantial. A secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) published in *JAMA Network Open* reports that angiotensin II receptor-stimulating, versus inhibiting, antihypertensive medications may confer a protective benefit on cognitive decline in older adults with high blood pressure. If confirmed in randomised trials angiotensin II receptor-stimulating medications may need to be prioritised in this population and prevention of cognitive impairment may even become an indication for antihypertensive treatment in older people. Results from a meta-analysis of randomised clinical trials may assist clinicians to weigh up the potential short-term side-effects of bisphosphonate therapy in postmenopausal women with osteoporosis against longer-term fracture risk reduction, finding it most likely to be of benefit only in patients with a life expectancy of at least one year. In Australia where the median survival of new entrants to residential care is close to the one-year mark this would translate to very little benefit of anti-resorptive therapy initiation but a high burden of gastrointestinal irritation. Finally, subcutaneous hydration demonstrates a non-inferior safety profile to intravenous administration in hospitalised patients and frailty after traumatic injury is associated with one-year mortality.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Associate Professor Peter Lange

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Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study

Authors: Mohile S et al.

Summary: Incorporation of geriatric assessment-guided management into palliative oncology care significantly reduces the burden of serious toxic adverse events and has other benefits including fewer falls according to results from the GAP70+ trial published in *The Lancet*. The cluster-randomised trial (ClinicalTrials.gov Identifier: NCT02054741) - a collaborative effort conducted by the US National Cancer Institute, the University of Chicago and the City of Hope National Medical Centre – enrolled 718 elderly (mean age of 77.2 years) patients with an advanced stage 4, incurable solid malignancy or lymphoma about to initiate a new treatment regimen from 40 US community oncology practice clusters. At baseline geriatric assessment all patients had a deficit in at least one of the evaluated domains of physical performance, functional status, comorbidity, polypharmacy, cognition, nutrition, social support, psychological status or cognition. Oncology practice clusters were randomised to receive individualised geriatric assessment summary plus management recommendations that covered dose-reductions (N=16/40) or usual care. At three months, significantly fewer patients in the intervention arm experienced a serious adverse event (grade 3-5 toxic adverse event, 51% vs 71%; relative risk 0.74; 95% confidence interval [CI],0.64-0.86; p=0.0001). This group also had significantly fewer falls (12% vs 21%; relative risk 0.58; 95% CI, 0.40-0.84; p=0.0035) and discontinued more medications (mean adjusted difference 0.14; 95% CI, 0.03–0.25; p=0·015).

Comment: Geriatric Oncology is advancing with the advent of well-designed trials such as this one, randomising patients that would commonly be seen in practice such as these with incurable solid organ tumours or malignancy and an impairment of a geriatric domain (we would consider this largely synonymous with a geriatric syndrome) to a structured, one-off intervention or not. Significant differences in outcomes important to our patients were observed, with a positive primary outcome of adverse effects of treatment. The devil is in the detail here – what is a geriatric assessment, how is it done, how are the results implemented, who can do it? Trials like these fill in this puzzle, though pieces are yet left.

Reference: Lancet 2021;398(10314):1894-1904

Abstract

Association of antihypertensives that stimulate vs inhibit types 2 and 4 angiotensin II receptors with cognitive impairment

Authors: Marcum Z et al., on behalf of the Systolic Blood Pressure Intervention Trial (SPRINT) Research Group

Summary: The SPRINT research group performed a secondary analysis of their two-arm randomised clinical trial (NCT01206062) to evaluate if as per the angiotensin hypothesis type 2 and 4 angiotensin II receptor-stimulating antihypertensive medications confer a lower risk of incident cognitive impairment versus angiotensin II receptor-inhibiting medications. Analysis was based on a cohort of 8,685 patients older than 50 years of age (mean age 67.7 years; 64.3% male) with elevated blood pressure (systolic blood pressure ≥ 130 mm Hg) and at least one risk factor for cardiovascular disease such as sub/clinical cardiovascular disease excluding stroke, chronic kidney disease and elevated Framingham Risk Score and/or age > 75 years undergoing anti-hypertensive treatment. Patients were stratified into three groups according to their antihypertensive medication regimen at six-months: exclusively angiotensin II receptor type 2 and 4–stimulating antihypertensives (n=2,644), angiotensin II receptor–inhibiting antihypertensives (n=1,536) or a mixed regimen containing medications from each class (n=4,505). At a median follow-up of almost five-years a significantly lower rate of a composite outcome measure of incident adjudicated amnestic mild cognitive impairment or probable dementia was found in the angiotensin II receptor-stimulating versus inhibiting cohort (45 vs 59 cases per 1,000 patient-years) with inverse probability of treatment–weighted Cox proportional hazards regression modelling revealing a 26% reduced risk (hazard ratio [HR] 0.76; 95% CI, 0.66-0.87). This finding was consistent when the outcomes were considered separately (amnestic mild cognitive impairment, HR 0.74; probable dementia, HR 0.80). The data suggests that prevention of cognitive impairment may become an indication for antihypertensive treatment in older patients.

Comment: This intriguing study investigates a hypothesis uniting some of the disparate ideas about the link between blood pressure treatment and dementia. Other studies have considered the timing of the hypertension and intervention as important, but a competing hypothesis is that the mechanism of blood pressure lowering is important. This study considers the effect of the agent. In a subset of the SPRINT trial (worthy of much discussion in and of itself), an association between use of medications that stimulate (angiotensin II receptor type 1 blockers, dihydropyridine calcium channel blockers, and thiazide diuretics) vs inhibit (angiotensin-converting enzyme [ACE] inhibitors, β-blockers, and nondihydropyridine calcium channel blockers) was sought. Secondary effects from medication agents that increase ACEII receptors type 2 and 4 stimulation might be involved in pathological mechanisms that increase risk of dementia. Here this was associated with an elevated risk, but residual confounding is possible, suggesting the effect of another unknown variable could account for the observed association, such as socio-economic or race factors that are associated both with dementia and use of certain medications for blood pressure control. While intriguing, this finding is for watching, not changing practise.

Reference: JAMA Netw Open 2022;5(1):e2145319
Abstract

Exploration of cognitive outcomes and risk factors for cognitive decline shared by couples

Authors: Yang H et al.

Summary: This Korean population-based, couple cohort study combined data from the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) study with data on their spouses to investigate if shared risk factors for cognitive disorders mediate the risk of cognitive impairment in older couples. A total of 784 older couples – 784 participants from the KLOSCAD study aged at least 60 years (39.2% female; mean age 74.8 years) plus their opposite-sex spouses (mean age 73.6 years) – who underwent bi-annual psychiatrist-conducted cognitive assessment for ten years (2010 to 2020) were included in the study. Cognitive disorders were significantly more prevalent in spouses with partners with cognitive disorders (38.8% vs 22.6%; $p<0.001$) with structural equation modelling analysis revealing the risk to be almost two-fold higher compared to spouses with a partner without a cognitive disorder (defined as mild cognitive impairment or dementia; odds ratio 1.74; 95% CI, 1.12-2.69; $p=0.01$). The relationship was mediated by a history of head injury, age and physical inactivity through major depressive disorder (β = 0.50, 2.57, 0.33 and 0.28, respectively).

Comment: Many of us have observed the challenge of a patient brought in for assessment for dementia and noted them to be merely the more impaired of the couple*! In previous studies of this phenomenon the association has been confirmed, though perhaps not to the extent observed in this cohort study showing twice the risk in the spouse of a participant with a cognitive disorder. Couples share common behaviours and often backgrounds, and it has been hypothesised that socio-economic background and cardiovascular risk behaviour was the cause of much of that association. In this study however, physical inactivity with major depressive disorder was a strong factor mediating the relationship, something that may be more amenable to intervention, perhaps even in later life. When we recommend exercise as a cognitive and/or mood intervention perhaps we should be recommending to both members of the couple. *Note this study exclusively examined heterosexual couples, which is a limitation.

Reference: JAMA Netw Open 2021;4(12):e2139765
Abstract

Time to benefit of bisphosphonate therapy for the prevention of fractures among postmenopausal women with osteoporosis

Authors: Deardorff W et al.

Summary: This meta-analysis of randomised clinical trials aimed to elucidate the minimum duration of prophylactic bisphosphonate therapy required to confer a clinical benefit in postmenopausal women with osteoporosis. The researchers fitted random-effects Weibull survival curves to data from 10 randomised clinical trials including over 23 thousand postmenopausal women with a primary diagnosis of osteoporosis (n=23,384; defined as existing vertebral fractures or bone mineral density T scores of ≤ −2.5; mean age 63-74 years) of alendronate, risedronate or zoledronic acid versus placebo with between one and four years of follow-up. Pooled random-effects meta-analysis showed that just over one year of treatment (12.4 months) conferred a benefit, preventing one nonvertebral fracture per 100 treated women at an absolute risk reduction threshold of 0.010. The magnitude of benefit increased with duration of therapy. Longer treatment duration was required to see a benefit in hip fracture prevention (20.3 months to prevent one hip fracture in 200 treated women).

Comment: A common clinical concern in the management of older patients with fracture is estimating the duration and survival and therefore the likelihood of benefit of adverse events of osteoporosis treatment. Received wisdom is that these agents require at least six months to benefit. This study contributes greatly to that analysis by unifying trials to estimate time to an absolute risk reduction of one non-vertebral fracture per 100 women, finding this was attained at 12.4 months. For comparison, this is very close to median survival of new entrants to residential care in Australia. Whilst an individualised decision, this study gives some baseline value from which to estimate an individual's risk. I found this study compelling, particularly the time to treat to prevent one hip fracture would be 20.3 months for 200 osteoporotic women. For many, this would mean little to no net benefit in initiating anti-resorptive therapy in the group entering a nursing home in Australia.

Reference: JAMA Intern Med 2022;182(1):33-41
Abstract

The bladder at night during hospitalisation: Towards optimal care for elderly patients with nocturia

Authors: Van Besien W et al.

Summary: This multisite, mixed methods cross-sectional study reports a high prevalence of nocturia in older hospitalised patients. The researchers utilised a standardised researcher-administered questionnaire to evaluate the burden and impact of nocturnal urinary incontinence in a cohort of 308 older patients hospitalised for at least two days. Despite most participants (84.4%) reporting experiencing nocturia, there was a substantial lack of general knowledge amongst patients and only one-fifth discussed it with a medical professional. Nocturia in the month preceding admission, high diurnal voiding frequency and nocturnal urinary urgency were all associated with nocturia during hospital admission. Interviews with a small cohort of patients (n=16) with ≥ two nocturia episodes per night found that nocturia caused quite a high burden especially on disrupted sleep and fear of falls.

Comment: Sleep disorders and incontinence are regarded as geriatric syndrome; both are highly prevalent. Falls are a frequent complication of hospitalisation and night time and urinary incontinence a common risk factor. This study looked at patient attitudes to nocturia and found the same nihilism that can affect medical staff about geriatric syndromes can affect patients, with most believing nocturia to be normal and not informing medical staff. Comprehensive falls prevention plans therefore, likely need to specifically ask about nocturia and intervene. Since most nocturia preceded admission, this is an opportunity to intervene in-hospital to improve the patient's quality of life at home.

Reference: Int J Clin Pract 2021;75(12):e14876
Abstract

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BAYER

Adverse effects of subcutaneous vs intravenous hydration in older adults: An assessor-blinded randomised controlled trial (RCT)

Authors: Danielsen M et al.

Summary: This Danish assessor-blinded, non-inferiority randomised trial enrolled geriatric patients (n=51) admitted to Aalborg University Hospital's emergency department, acute assessment unit or orthopaedic unit to assess the safety of subcutaneous versus intravenous administration of parenteral hydration. Patients were administered 0.5-2 litres of parenteral fluid over the next 24 hours by one of the two routes (subcutaneous, n=24; intravenous, n=27) with sham catheters to maintain blinding. The trial demonstrated subcutaneous to be non-inferior to intravenous for safety outcomes with no significant difference between trial arms in the incidence of adverse events within 24-hours (p=0.012). The authors also found that subcutaneous catheters insertion was significantly faster than intravenous.

Comment: Subcutaneous hydration has perhaps not received the attention it deserves in terms of scientific study. Older studies with methodological shortcomings that would be considered unacceptable today form the bulk of evidence. This trial was blinded, randomised, with clear inclusion and exclusion criteria that permit an understanding of how participants and therefore, the results can be relevant to clinical practice. They randomised patients to subcutaneous fluids or intravenous fluids and blinded the assessors to that status. The patients were mildly dehydrated needing 1-2 L of fluid per day. This trial, though regrettably stopped early, did show that subcutaneous fluid could run at a high rate (q6-8h) when placed on the abdomen. I could not determine the constituent of the fluid. Though stopped early due to problems with enrolment, the rate of adverse events was no worse. I would like to see more studies so that perhaps, I could change practise.

Reference: Age Ageing 2022;51(1):afab193
Abstract

Predicting 1 year mortality after traumatic injury using the Clinical Frailty Scale

Authors: Braude P et al.

Summary: This observational study assessed the impact of frailty at the time of traumatic injury on one-year mortality in geriatric patients. The study cohort was comprised of 585 patients over the age of 65 years (median age 81 years) admitted to the Severn Major Trauma Network's major trauma centre in England with a traumatic injury (median injury severity score 13) between November 2018 and September 2019. Frailty was assessed at hospitalisation by a geriatrician using the Clinical Frailty Scale (CFS). At one-year follow-up one quarter of the cohort had died. Multivariable Cox proportional hazards model analysis adjusted for age, sex, multimorbidity, surgery, most injured site, injury severity, postinjury complications and geriatrician review found a positive relationship between frailty severity and mortality. Compared to patients with a baseline CSF score of 1-3, vulnerable/very mildly frail patients (CFS 4) had an almost two-fold higher risk of mortality and severely frail patients (CSF 7-8) had a more than six-fold increased risk.

Comment: The CFS has achieved much popularity due to (relative) robustness, ease of use and applicability in a variety of contexts, including trauma. In this study, CFS at admission administered by a geriatrician had a strong relationship with one-year mortality. The challenge is to use CFS to direct interventions appropriately, be that increased intervention to those at risk of death or potentially to identify a group at such likelihood of death that intervention would be burdensome. CFS should be regarded at most as a screening tool to identify patients who will benefit from Comprehensive Geriatric Assessment, rather than an intervention in and of itself.

Reference: J Am Geriatr Soc 2022;70(1):158-67
Abstract

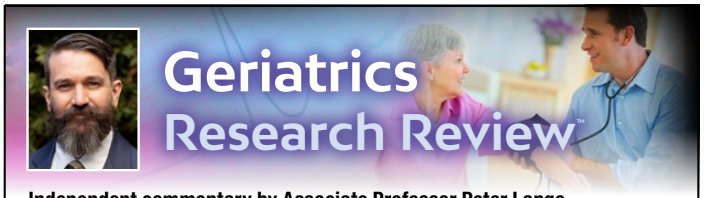
Association between dietary protein intake and change in grip strength over time among adults of advanced age: Life and Living in Advanced Age: A Cohort Study in New Zealand (LiLACS NZ)

Authors: Wham C et al.

Summary: Carol Wham and colleagues analysed data from 554 octogenarians in the New Zealand LiLACS study to investigate if dietary protein intake might benefit physical function as measured by grip strength. Study participants were elderly indigenous Māori people born between 1920 and 1930 or non-Māori New Zealanders born in 1925. The study reported a low protein intake with daily weight-adjusted intakes ranging from 0.98-1.05 g/kg in men and 0.87-0.91 g/kg in women. Grip strength reduced over the five-year follow-up with annual percent reductions of 2.38 and 5.47 in Māori women and men, respectively and 4.49 and 1.81 in non-Māori women and men. The authors concluded that protein intake did not protect against loss of grip strength.

Comment: Sarcopenia (often measured with grip strength) is associated with many poor outcomes in older persons and interventions in protein intake have shown promise over time. Older recommendations for protein intake of approximately 1 g/kg bodyweight/day have been revised up as evidence of poor protein absorption and utilisation in skeletal muscle continues, with suggestions to increase by 20% in individuals over 70 years of age. Here, many participants were consuming below recommendations. Grip strength declined over time. Other studies have shown that grip strength is associated with protein intake, and changes in grip strength are associated with protein intake. The apparently contradictory findings are likely due to the difficulty in studying these conditions with measurement tools that are not so precise and accurate. Overall, the evidence is good that even previously recommended protein intake is inadequate for older people.

Reference: Australas J Ageing 2021;40(4):430-37
Abstract



Independent commentary by Associate Professor Peter Lange.

Peter Lange completed a Bachelor of Science degree at the University of Queensland, majoring in physiology and pharmacology. He then completed postgraduate medicine, obtaining an MBBS, internship and early years of training in Queensland. He came to Melbourne in 2005 where he completed physician and geriatrics advanced training at the Royal Melbourne Hospital. He commenced work both in the General Medicine and Geriatrics departments in 2010. In 2012 he was appointed head of the Assessment and Planning Unit at RMH, later renamed the Acute Medical Unit where he was Head of Unit until 2021.

In 2016 he took up a PhD with the topic "Delirium in Hospitalised Elderly; changing the Natural History" at the University of Melbourne, representing the formalisation of a research interest in delirium.

In 2019 he was appointed Honorary Clinical Associate Professor of the University of Melbourne.

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