FATIGABILITY: AN EARLY MARKER OF DIMINISHED RENAL FUNCTION?

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Renal function declines markedly with age due to normal aging and/or disease processes and impacts multiple systems. Diminished renal function may manifest as low exercise tolerance and fatigue threshold. Using data on 951 well-functioning (usual gait speed >.67m/s and no difficulty walking ¼ mile) men and women (51%) aged 60-89 years in the Baltimore Longitudinal Study of Aging, we evaluated the cross-sectional association between perceived fatigability (Rating Perceived Exertion after 5-minute treadmill walk at 1.5mph) categorized as 6-7, 8-9, 10-11 and 12+ and GFR using Cockcroft-Gault. For each fatigability increment, likelihood of suboptimal (GFR=75-89, 21%), diminished (GFR=60-74, 26%) and poor renal function (GFR<60, 30%) relative to GFR≥90 was respectively OR(95%CI) p-value 1.51(1.16-1.96).002, 1.38(1.04-1.83).027 and 1.68(1.22-2.31).002 adjusted for demographics, weight, height, smoking, exercise and anemia. Findings were similar for men and women. Perceived fatigability may facilitate identification of apparently well-functioning older adults on the precipice of suboptimal to poor renal function.

ASSOCIATION BETWEEN ARTERIAL STIFFNESS AND FATIGABILITY IN WELL-FUNCTIONING OLDER ADULTS

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The association between vascular health measured by arterial stiffness and fatigability, a marker of future mobility decline, is unknown. We examined 1210 men (47.7%) and women from the Baltimore Longitudinal Study of Aging, mean age 66.6±13.9 years. Perceived fatigability was assessed after a 5-minute, treadmill walk using Borg rating (range 6-20). Arterial stiffness was determined by carotid femoral pulse wave velocity (PWV). In linear regression analyses fatigability and PWV were associated in men (Beta/P-value) (0.160/0.001) and women (0.136/0.008). Adjustment for mean arterial and pulse pressure attenuated the association in women (0.104/0.050) but not men (0.160/0.001). The association was significant among those with slower usual and rapid gait speeds, longer 400m walk time and slower repeated chair stands pace (all p<0.05). Arterial stiffness is associated with a greater proneness to fatigue especially in older adults exhibiting poorer mobility. The underlying mechanisms appear to differ between men and women.

ASSOCIATIONS BETWEEN PERCEIVED FATIGABILITY AND AMYLOID STATUS IN THE BALTIMORE LONGITUDINAL STUDY OF AGING

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Higher level of and greater longitudinal increase in perceived fatigability are linked to cognitive decline and lower brain volumes in older adults. However, it remains unclear whether perceived fatigability is associated with Alzheimer’s disease-related brain pathology. In the BLSA, 163 participants without neurological disease or cognitive impairment (aged 74.7±8.4 years, 45% men) were assessed for perceived fatigability using rating of perceived exertion after a 5-minute (0.67 m/s) treadmill walk and Aβ burden using 11C-Pittsburgh compound B (PiB) positron emission tomography. Forty-four participants were PiB+ based on a mean cortical distribution volume ratio (DVR) cut point of 1.066. After adjusting for demographics, body composition, comorbidities and ApoE-e4, higher perceived fatigability was not associated with PiB+ status (OR=0.84; 95% CI: 0.69, 1.05). Results suggest perceived fatigability may contribute to cognitive decline through pathways other than Aβ...
pathology. Future studies should target other mechanisms linking perceived fatigability and cognitive decline.

LONGITUDINAL ASSOCIATION BETWEEN PERCEIVED FATIGABILITY AND BRAIN VOLUMES IN COMMUNITY-DWELLING OLDER ADULTS

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Perceived fatigability is linked to declining physical and cognitive performance, yet whether fatigability reflects early subclinical change in brain structure is unknown. Using mixed effects models, we assessed the longitudinal association of 3T MRI-derived brain volumes with perceived fatigability after a 5-min treadmill walk (0.67 m/s, 0% grade) using the Borg Rating of Perceived Exertion scale (range 6-20) in 802 BLSA participants (age 68.2+/−12.4 years, 45% men 66% White). In models adjusted for intracranial volume, demographics, chronic conditions, and CESD score, declining gray matter volumes in the frontal (β=-0.01) and temporal (β=-0.02) lobes, as well as the hippocampus (β=-0.25), precuneus (β=-0.10) and thalamus (β=-0.19) were associated with higher fatigability. Larger ventricular volumes were also associated with higher fatigability (β=0.02). Brain atrophy, particularly in gray matter and the hippocampal region, is longitudinally associated with increased fatigability in cognitively normal older adults, making it a potential marker of brain atrophy.

Session 2290 (Symposium)

PROSPECTIVE MONITORING OF NEWLY MARKETED DRUGS IN FRAIL OLDER ADULTS USING REAL-WORLD DATABASES

Chair: Dae Kim Co-Chair: Elisabetta Patorno

In recent years several new drugs have been approved for treatment of heart failure and type 2 diabetes. Despite their life-prolonging benefits, uptake of new drugs is often slow among older patients with frailty due to under-representation of frail older adults in pivotal clinical trials and concerns for adverse events. To optimize pharmacotherapy, timely evaluation of the drug benefits and risks is urgently needed. We propose a novel drug monitoring framework that prospectively evaluates the effectiveness and safety of newly marketed drugs for frail and non-frail patients in real-world databases. This framework utilizes a validated claims-based frailty index (CFI) (range: 0-1; frail if ≥0.20) to find early signals for effectiveness and safety of new drugs by updating the analysis at regular intervals as new data become available. In this symposium, we present early results of this prospective monitoring framework for 2 new drug classes using Medicare claims data from the approval date until the end of 2017: 1) angiotensin receptor-neprilysin inhibitor (ARNI) (approved in July 2015) for heart failure with reduced ejection fraction (HFrEF) and 2) sodium-glucose cotransporter-2 inhibitors (SGLT2i) (approved in March 2013) for type 2 diabetes. We first show the uptake of ARNI and SGLT2i over time among the eligible Medicare beneficiaries by clinical characteristics, including frailty. Subsequently we present the results of sequential cohort analysis for the effectiveness and safety results of ARNI and SGLT2i. After these presentations, the panel will discuss the strengths, limitations, and challenges of implementing our monitoring framework in real-world databases.

MONITORING THE EFFECTIVENESS AND SAFETY OF ARNI VS. ANGIOTENSIN RECEPTOR BLOCKER BY FRAILTY STATUS

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Using Medicare data 2015-2017, we conducted 5 sequential 1-to-1 propensity score-matched analyses of ARNI initiators and angiotensin receptor blockers (ARB) initiators, mimicking the accrual of new data every 6 months. Primary effectiveness endpoint was a composite of heart failure hospitalization or all-cause mortality and primary safety endpoint was a composite of hospitalization or emergency department visits for hypotension, acute kidney injury, hyperkalemia, and angioedema. Among non-frail patients (n=5,014), the rates (per 100 person-years) for ARNI vs ARB were 12.7 and 9.2 (rate difference: 3.4, 95% CI: 0.8 to 6.1), respectively, for the effectiveness endpoint and 5.2 and 3.6 (rate difference: 1.5, 95% CI: -0.1 to 3.2), respectively, for the safety endpoint. Among frail patients (n=2,694), the corresponding rates were 19.8 and 21.6 (rate difference: -1.8, 95% CI: -7.0 to 3.4) for the effectiveness endpoint and 10.9 and 8.0 (rate difference: 2.9, 95% CI: -0.6 to 6.4) for the safety endpoint.

MONITORING THE COMPARATIVE SAFETY OF SGLT2I VS GLP-1 RA IN OLDER ADULTS WITH TYPE 2 DIABETES BY FRAILTY STATUS

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Using Medicare data (4/2013-12/2017), we conducted 9 sequential analyses of patients with type 2 diabetes initiating SGLT2i vs. GLP1-RA mimicking the accrual of new data every 6 months to monitor SGLT2i safety with respect to diabetic ketoacidosis (DKA) since their U.S. approval. For each analysis, we estimated cumulative HRs (95% CIs) after 1:1 propensity score matching on >70 covariates comparing treatments within frail and non-frail patients. By analysis 1, SGLT2i were associated with a higher DKA rate vs. GLP1-RA in both frail and non-frail patients, but results were highly imprecise due to few events. With the accrual of more DKA events, precision of the estimates continued to improve through analysis 9 [HR=2.95 (95% CI, 1.19-7.31)] in frail patients; [HR=1.77 (1.15, 2.75)] in non-frail patients], with sufficiently precise estimates by analysis 6 in frail patients [HR=2.80 (95% CI, 1.03, 7.61)] and by analysis 7 in non-frail patients [HR=1.62 (95% CI, 1.01, 2.57)].