

# REHAB IN REVIEW

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## WEEKEND WARRIORS AND CARDIOVASCULAR DISEASE

The current World Health Organization and American Heart Association guidelines recommend 150 minutes or more of moderate to vigorous physical activity (MVPA) per week. The distribution of this activity throughout the week necessary to obtain these health benefits is not clear. This study used wrist worn accelerometers to better understand this issue.

Data were obtained from the United Kingdom Biobank, a prospective cohort of a 502,629 participants 40 to 69 years of age. Wearable monitors were used to determine the amount, intensity, and time of the activity. These data were used to classify individuals as active (A: over 150min/week of MVPA) or inactive (IA: under 150 min/week of MVPA). The A group was further classified as weekend warriors (WW; over 50% of the total MVPA occurring over one to two days) or active regular (AR over 50% of the MVPA distributed over more than two days). The data were analyzed to determine the association between these activity patterns and incident atrial fibrillation, myocardial infarction, heart failure, and stroke.

Data were analyzed for 89,573 individuals, with 42.2% in the WW group, 24% in the AR group, and 33.7% in the IA group. An adjusted analysis revealed that, compared to the IA group, both the AR and WW groups had similarly low risks of incident atrial fibrillation, myocardial infarction, heart failure, and stroke.

**Conclusion:** This study demonstrates that the health benefits of moderate to vigorous physical activity are similar when this activity is condensed into a weekend compared to distribution over the entire week.

Khurshid, S, et al. Accelerometer Derived Weekend Warrior Physical Activity and Incident Cardiovascular Disease. *JAMA*. 2023, Jul 18; 330(3): 247-252.

## CIRCULATING PROTEOME AND OSTEOARTHRITIS TRAITS

The human plasma proteome consists of proteins that are secreted or shed into the circulation to either carry out a function or to mediate cross tissue communication. These proteins are frequently dysregulated in disease, thus becoming important targets of drug intervention. This study was designed to identify proteins that might be related to the progression of OA, and thus potential targets of medical intervention.

Data were obtained from previous large scale proteomic studies of circulating proteins, which identified the protein quantitative trait loci (pQTLs) of the proteins. Mendelian randomization was used to quantify the exposure-outcome relationship between the different proteins and OA. This was completed for 12 separate traits of OA.

The analysis found 26 unique proteins that were causally associated with at least one OA trait. Of those, 14 proteins were found to be the target of existing or potential drugs.

**Conclusion:** This study, using a unique analysis of circulating proteins, found new circulating proteins that are causally associated with osteoarthritis-related traits.

Zhang, Y., et al. Evaluating the Causal Effect of Circulating Proteome on the Risk of Osteoarthritis-Related Traits. *Ann Rheum Dis*. 2023, August 18. doi: 10.1136/ard-2023-224459.

## IMPLANTABLE SHOCK ABSORBER FOR KNEE OSTEOARTHRITIS

Among younger patients with knee osteoarthritis (OA) who fail conservative treatment and undergo total knee arthroplasty (TKA), over a third report residual symptoms and functional limitations within the first year post-surgery. An implantable shock absorber (ISA) has been developed to unload the knee, placed

in the extracapsular space, superficial to the medial collateral ligament, in an outpatient procedure. This study assessed the survivorship of this device.

Data were obtained from three, prospective, multicenter, single arm, clinical trials, comprising 171 subjects who received the ISA. The participants were 25 to 65 years of age with symptomatic OA in the target knee after six or more months of conservative treatment. The primary efficacy outcome was five-year survival without arthroplasty or high tibial osteotomy (HTO).

At a mean follow up of 3.2 years, 155 of the 171 subjects had survived without undergoing arthroplasty or HTO. From baseline to follow-up WOMAC pain scores decreased from 58 to 16 points ( $p < 0.0001$ ). Over that same time, the WOMAC-Function scores improved from a mean of 56 to 17 points ( $p < 0.0001$ ).

**Conclusion:** This study of patients with knee osteoarthritis, resistant to conservative treatment, found that a reversible, implantable shock absorber was effective in reducing pain and increasing function.

Gomoll, A., et al. An Implantable Shock Absorber Yields an 85% Survival from Arthroplasty Rate through Five Years in Working Age Patients with Medial Compartment Knee Osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2023, August; 31(8): 3307-3315.

## PHYSICAL ACTIVITY AND KNEE JOINT SPACE LOSS OVER TWO YEARS

Studies of the effect of physical activity on the progression of osteoarthritis (OA) of the knee have produced mixed results. This study evaluated the association between the intensity of movement during physical activity and the progression of OA of the knee.

Subjects were adults with OA, 45-79 years of age, enrolled at study sites in Columbus, Ohio, Baltimore,

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Maryland, Pittsburgh, Pennsylvania, and Pawtucket, Rhode Island. The physical activity (PA) was determined using an actigraph monitor with the subjects placed into mutually exclusive categories. These included moderate-to-vigorous PA (MVPA), light PA (LPA), and sedentary time (SED). The outcome was a change in radiographically demonstrated medial joint space width (JSW) over two years.

Data were collected for 969 participants with a mean age of 64.5 years. Using adjusted regression models, higher MVPA was not associated with greater medial JSW loss (p= 0.97), nor was LPA (p= 0.27) or SED (p= 0.21).

**Conclusion:** This study failed to demonstrate that physical activity, either the vigorous or light, was associated with an increased joint loss among patients with osteoarthritis of the knee.

Voinier, D., et al. Association of Physical Activity with Loss of Knee Joint Space Width Over Two Years: A Compositional Data Analysis in the Osteoarthritis Initiative. **Osteoarthritis Cartilage.**2023;31(8): 1091-1100.

**CONDUCTION STUDIES VERSUS ULTRASOUND COMPARED TO SYMPTOMS IN CARPAL TUNNEL SYNDROME**

Several reports have found that the severity of symptoms reported by patients with carpal tunnel syndrome (CTS) is poorly correlated with the physiologic impairment measured by neurophysiological methods. Ordinary neurophysiological methods do not measure ectopic action potentials and tell us nothing about small-fiber function. As ultrasound (US) is gaining in popularity as a diagnostic tool, this study compared patient symptoms with the results of US and neurophysiologic testing.

Patients were identified from the Canterbury CTS database. All participants completed the Boston Carpal Tunnel Questionnaire at the time of their presentation for suspected CTS. This database includes information about the symptom pattern, medical history, and outcome of tests including ultrasound and neurophysiologic measures. The severity of median nerve impairment in each hand was determined using the Canterbury CTS severity scale and neurophysiologic scale of CTS severity. For those who had an US examination, the right- and left-side

cross-sectional area (CSA) measurements were extracted.

Data were available for 433 patients with bilateral US measurements as well as neurophysiologic measurements. The data revealed a significant relationship between right-hand NCS grade and symptom severity score (p< 0.001). No correlation was found between right-hand cross-sectional area and symptom severity.

**Conclusion:** This study of patients with carpal tunnel syndrome found a significant relationship between symptomatic and electrophysiologic severity, which was stronger than the correlation of symptoms with ultrasound imaging.

Fargaly, S., et al. Do Nerve Conduction Studies or Ultrasound Imaging Correlate More Closely with Subjective Symptom Severity in Carpal Tunnel Syndrome? **Musc Nerve.** 2023, September; 68 (3): 264-268.

**AURICULAR VAGUS NERVE STIMULATION FOR INSOMNIA**

Insomnia Disorder (ID) is defined as poor quality or insufficient sleep. The etiology of ID is often associated with dysfunction of the thalamus. This study used functional resting state magnetic resonance imaging (fMRI) to focus on abnormal functional connections (FCs) between the bilateral thalamus and the anterior cingulate gyrus and bilateral insula (the salient network), the insular and dorsal cingulate gyrus (the negative emotion network), and the frontoparietal network (default mode network). Transcutaneous auricular vagus nerve stimulation (taVNS) was used to determine whether these FCs might be susceptible to modulation.

A Hwato brand electronic acupuncture instrument was used for intervention. The pulse frequency was adjusted to 20 Hz for bilateral taVNS for 30 minutes in twenty patients. Functional magnetic resonance imaging (fMRI) data were collected immediately before and then after taVNS treatment. Twenty age and gender-matched controls were scanned for comparison.

Prior to taVNS the fMRI demonstrated increased levels of glucose metabolism, suggesting an increased resting state functional connectivity (RSFC), as well as a high arousal in patients with ID. After treatment with taVNS, the RSFC between the thalamus and right angular gyrus, anterior cingulate

gyrus, and precuneus decreased, resulting in improved arousal.

**Conclusion:** This study found that the changes in the functional connection between the thalamus and the right angular gyrus, left anterior cingulate gyrus, and precuneus seem to be the basis for the treatment of insomnia disorder with taVNS.

Zhao, B., et al. Altered Functional Connectivity of the Thalamus in Patients with Insomnia Disorder after Transcutaneous Auricular Vagus Nerve Stimulation Therapy. **Front Neurol.** 2023, Jul 6;14:1164869.

### MIND DIET AND COGNITIVE PRESERVATION

Previous studies have suggested that dietary patterns may be protective against cognitive decline. This study assessed the efficacy of a hybrid of the Mediterranean and the Dietary Approaches to Stop Hypertension (DASH) diet, known as the MIND diet, in slowing cognitive decline.

This randomized, controlled trial included persons  $\geq 65$  years of age with scores of at least 22 on the 30-item Montreal Cognitive Assessment (MOCA), who had a body mass index of  $\geq 25$  kg/m<sup>2</sup>, reported a family history of Alzheimer's dementia, and had suboptimal diets. The subjects were assigned to the MIND diet with mild caloric restriction for weight loss (goal of intake was to consume 250 kcal less per day) or their usual diet with the same mild caloric restriction for weight loss (control diet). The participants were instructed to follow their assigned diet for three years, with data points at month six and then yearly until year three. The primary endpoint was the change from baseline in global cognition and in specific cognitive domains through year three.

Data were collected from 301 participants in the MIND diet group and 303 in the control diet group. From baseline through year three, the mean changes in global cognition scores of those in the MIND diet group were not significantly different from those in the control diet group ( $p=0.23$ ). At the end of the trial, white-matter hyperintensity volumes increased to a similar extent in both the MIND diet group and the control group. In addition, the decrease in total brain volumes and volumes in the hippocampus were similar between the two groups.

**Conclusion:** This study of patients 65 years of age or older

found that improvements in cognition did not differ significantly between those who followed the MIND diet and those who followed a control diet with mild caloric restriction.

Barnes, L., et al. Trial of the MIND Diet for Prevention of Cognitive Decline in Older Persons. **N. Eng J Med.** 2023, Aug 17; 389(7): 602-611.

### ALGINATE GEL IMPLANTATION FOR KNEE CHONDRAL DEFECTS

Among the interventions designed to repair chondral lesions are bone stimulation techniques (BMSTs) for lesions  $< 2$  cm<sup>2</sup>. This small study assessed the efficacy of an injectable ultra purified alginate (UPAL) gel as a bioactive scaffold to assist with cartilage regeneration.

The subjects were 12 patients with isolated, full thickness cartilage defects of the knee, 1-4 cm<sup>2</sup>. After debridement and bone marrow stimulation of the cartilage lesion, the defects were filled with a UPAL solution. Post-operative rehabilitation allowed non-weight bearing for the first two weeks, partial weight bearing after two weeks, and full weight bearing at four weeks. The patients were assessed for up to 144 weeks postoperatively using leucocyte counts, serum C-reactive protein levels, a visual analogue scale (VAS) for pain, and the Knee Injury and Osteoarthritis Outcome Scores (KOOS). At 72 weeks, a second look arthroscopy was performed in 11 patients.

Significant improvements were noted from baseline to three years postoperatively in the mean VAS score for pain, the International Knee Documentation Committee Subjective Form, and five KOOS subscores ( $p<0.05$  for all). The MRI follow-up and arthroscopic follow-up demonstrated improvements in the International Cartilage Regeneration and Joint (ICRS) grade from III or IV to I or II, except in one case classified as grade III on both observations. Histological examination of the biopsy specimens of the repair material obtained at 72 weeks, demonstrated an extracellular matrix rich in glycosaminoglycan and type II collagen.

**Conclusion:** This study of patients with full thickness cartilage defects of the knee found that an ultra-purified alginate implantation can facilitate cartilage repair.

Onodera, T., et al. Single-Step, Ultra-Purified Alginate Gel Implantation in

Patients with Knee Chondral Defects: A Single Arm, Clinical Trial. **Bone Joint J.** 2023, August; 105-B (8): 880-887.

### OSTEOARTHRITIS, PHYSICAL PERFORMANCE AND QUALITY OF LIFE

Osteoarthritis (OA) is a complex, slowly evolving disease that is a leading cause of disability globally. As there is limited data on the significance of OA in Greece, this study was designed to quantify the pain and physical impairment experienced by those with difficult to treat, moderate to severe OA.

The PONOS study was a non-interventional, cross-sectional, epidemiologic study of Greek adult patients with symptomatic hip or knee (OA) of moderate to severe grade (Kellgren-Lawrence grade 2-3). Included were patients who were insufficiently improved with the use of paracetamol, nonsteroidal anti-inflammatory drugs, or opioids. Data were gathered concerning demographics, common clinical characteristics, comorbidities, and medications. Additional data involved patient-reported outcome measures, including the Hip disability and Osteoarthritis Outcome Score (HOOS), the Knee Injury and Osteoarthritis Outcome Score (KOOS), and the EuroQol-5-Dimensions 3-Levels Questionnaire.

The subjects were 164 patients from nine outpatient clinics in Athens, Greece. The mean BMI was 28.2, classified as "overweight". Ninety-two out of 164 patients (56.1%) had knee OA, 66 (40.2%) had hip OA, and six (3.7%) had OA in both joints (hip and knee).

Both hip and knee OA patients demonstrated a substantial deterioration in health-related quality of life. The HOOS subscale indicating the greatest impairment was in function in sport and recreation. Also noted was a substantial deterioration in self-perceived, overall health status, of patients with knee OA, reflected by a mean EQ-VAS score of 52.1. Physical disability was endorsed by two thirds of the patients.

**Conclusion:** This Greek study of adults with symptomatic hip or knee osteoarthritis of moderate to severe grade found that these patients had impairments in both functional ability and quality of life.

Savvari, P., et al. The Impact of Moderate to Severe Osteoarthritis on the Physical Performance and Quality

of Life: A Cross-Sectional Study in Greek Patients (PONOS Study). **BMC Musculoskel Disord.** 2023; 24 (1): 651.

### PLATELET-RICH PLASMA FOR ANKLE OSTEOARTHRITIS

Treatment options for patients with ankle osteoarthritis (AOA) are limited. A recent systematic review of the efficacy of platelet-rich plasma (PRP) for knee OA reported significant improvements in pain, function, and stiffness at 12 months. This study reviewed the effectiveness of PRP for patients with AOA.

This double-blind, placebo-controlled trial included 100 patients presenting with AOA and a pain severity of at least 40 on a 100-millimeter visual analog scale (VAS), with radiographs indicating a grade two or greater OA at the talocrural joint. The patients were randomized to a placebo group with saline injections or a PRP group. All subjects received one injection at inclusion and a second at six weeks. Questionnaires were sent at baseline and at six, 12, 26, 39, and 52 weeks. The primary outcome measure was the patient-reported portion of the American Orthopedic Foot & Ankle Society (AOFAS) score.

At 52 weeks, an adjusted analysis found that the AOFAS scores were more improved in the placebo group than in the treatment group ( $p=0.31$ ). No statistically significant between-group differences were found for improvement in any of the secondary outcome measures at 52 weeks.

**Conclusion:** This double-blind, randomized, placebo-controlled, clinical trial of patients with ankle osteoarthritis found that platelet-rich plasma injections did not improve patient reported outcome.

Paget, L., et al. Platelet-Rich Plasma Injections for the Treatment of Ankle Osteoarthritis. **Am J Sport Med.** 2023, August; 51(10): 2625-2634.

### INTRAARTICULAR MESENCHYMAL STEM CELLS FOR KNEE OSTEOARTHRITIS

Recent studies of osteoarthritis (OA) have found that inflammation, oxidative stress, growth factor, and the cytokine-mediated signaling pathway play a crucial role in its progression as the balance of anabolic and catabolic activities is compromised. Mesenchymal stem cells are thought to have paracrine effects which may skew the

biochemical environment of OA into regenerative and anti-inflammatory conditions. This study assessed the effect of intraarticular injections of autologous, culture-expanded, adipose-derived mesenchymal stem cells (ADMSCs).

This double-blind, placebo-controlled trial included patients 20 years of age or older with grade three osteoarthritis, based on American College of Rheumatology criteria, a pain intensity of  $\geq 50/100$  mm visual analog scale (VAS), and functional impairment of  $\geq 40$  on the Western Ontario and McMaster University of Osteoarthritis Index (WOMAC). All subjects were assessed by physical examination and laboratory tests before randomization. The stem cells were prepared after lipoaspiration. The patients were randomized to receive either autologous ADMSCs ( $1 \times 10^8$  ADMSCs; normal saline, 2.1 mL; autologous serum, 0.9 mL) or saline (normal saline, 2.1 mL; autologous serum, 0.9 mL).

Data were assessed for 125 patients in the treatment group and 127 in the placebo group. At six months, improvements in the treatment group were significantly greater than those in the placebo group in VAS pain scores and total WOMAC scores ( $p=0.004$  and  $p=0.002$ , respectively).

**Conclusion:** This study of patients with grade 3 osteoarthritis of the knee found that intra-articular injection of autologous, culture-expanded, adipose-derived mesenchymal stem cells could improve pain and function at six months.

Kim, K., et al. Clinical Efficacy and Safety of the Intra-articular Injection of Autologous Adipose-Derived Mesenchymal Stem Cells for Knee Osteoarthritis: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial. **Am J Sports Med.** 2023 Jul;51(9):2243-2253.

### INTERHOSPITAL TRANSFER TIME OF STROKE PATIENTS

For patients who present to an emergency department with symptoms of an acute ischemic stroke, (IS) interhospital transfer is often required to ensure access to time dependent care. As time from symptom onset to treatment onset is critical, this study reviewed the transfer times documented in a contemporary sample of United States hospitals.

Data were maintained in the *Get with the Guidelines Stroke Registry*,

an ongoing national database maintained by the American Heart Association/ American Stroke Association. The database included records of patients hospitalized for acute IS or hemorrhagic stroke (HS) who were transferred from the emergency department of one hospital to another acute care hospital. The primary outcome was time from emergency department presentation (door-in) to transfer out (door-out) of the emergency department to travel to another hospital.

Data were analyzed for 108,913 patients with a mean age of 66.7 years. The most common reasons for transfer were advanced stroke care (70.7%) and evaluation for endovascular therapy (20.3%). The median door-in door-out time was 174 minutes, including 132 minutes for patients with IS, eligible for endovascular therapy, and 178 minutes for patients with HS. Among those factors associated with longer transfer times were,  $>80$  years of age, female gender, non-Hispanic, Black versus non-Hispanic White, and Hispanic versus non-Hispanic White. Items associated with a shorter door-in door-out transfer time included emergency medical service prenotification, National Institutes of Health Stroke Scale scores exceeding 12, and eligibility for endovascular therapy versus hemorrhagic stroke.

**Conclusion:** This study of patients admitted to the emergency room with a diagnosis of acute stroke found that the median time from presentation to transfer to another hospital was 174 minutes, longer than the current recommendation for acute stroke transfer.

Stamm, B., et al. Door-In Door-Out Times for Interhospital Transfer of Patients with Stroke. **JAMA.** 2023, August 15; 330(7): 636-649.

### PITAVASTATIN TO PREVENT CARDIOVASCULAR DISEASE IN HIV

Previous studies have demonstrated that the risk of atherosclerotic cardiovascular disease, as well as stroke, is significantly elevated among persons with human immunodeficiency virus (HIV) infection. This phase three, Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) was designed to determine whether statin use can prevent atherosclerotic cardiovascular disease events in

persons with HIV at low to moderate risk.

The subjects were adults, 40 to 75 years of age, with a diagnosis of HIV infection, undergoing stable antiretroviral therapy. All were assessed as being at low to moderate risk of atherosclerotic cardiovascular disease. The participants were randomized to receive oral pitavastatin at four mg or an identical placebo once per day. Randomization was stratified according to gender and CD4 count. The primary outcome variable was the occurrence of major, adverse cardiovascular events, which included a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral artery disease, revascularization of a coronary, carotid, or peripheral artery, or death from an undetermined cause.

Data were gathered for 6,452 participants with a median age of 50 years and a median follow-up of 5.1 years. A major, adverse cardiovascular event was noted in 4.81/1,000 person-years in the pitavastatin group and 7.32/1,000 person-years in the placebo group ( $p=0.002$ ). The incidence of a first stroke or TIA was 1.56/1,000 person-years in the pitavastatin group and 2.36/1,000 person-years in the placebo group (relative risk (RR) 0.66).

**Conclusion:** This prospective study of patients with HIV found that those treated with pitavastatin had a significantly reduced risk of major cardiovascular events.

Grinspoon, S., et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. *N Engl J Med*. 2023, August 24; 389(8): 687-699.

### DELAYED PHYSICAL THERAPY AND OPIOID USE IN KNEE OSTEOARTHRITIS

The global opioid crisis has been partly fueled by the need to manage chronic musculoskeletal pain. Exercise is usually recommended as a first line treatment for osteoarthritis (OA). As evidence suggests that greater involvement by physical therapy (PT) can improve outcomes, this study assessed the association of the timing of PT initiation with subsequent opioid use.

Subjects were individuals  $\geq 40$  years of age with incident knee OA. Data were obtained from the Optum Labs data warehouse, which includes medical, pharmacy, therapy, and laboratory records for commercial

and Medicare Advantage enrollees. The primary outcome variable was the timing of PT initiation relative to the date of the diagnosis of OA.

Data were analyzed from the records of 67,245 patients. Among those who were opioid naive at baseline, the prevalence of any opioid use after the diagnosis of OA was 12.3%. Compared to those who initiated PT within one month of the diagnosis, the relative risk of any opioid use increased with the delay of PT. Compared to no delay, the relative risk (RR) of opioid use was elevated in those who initiated at one to under three months (RR 1.18), three to under six months (RR 1.49), six to under nine months (RR 1.73), and nine to 12 months (RR 1.93).

**Conclusion:** This study of persons with newly diagnosed knee osteoarthritis found that delaying the initiation of physical therapy beyond one month resulted in an increased risk of opioid use.

Kumar, D., et al. Delayed Timing of Physical Therapy Initiation Increases the Risk of Future Opioid Use in Individuals with Knee Osteoarthritis: A Real World, Cohort Study. *Br J Sports Med*. 2023, August; 57 (15):958-964.

### THETA BURST STIMULATION FOR UPPER LIMB RECOVERY AFTER STROKE

An increase in the inhibitory drive from the contralateral to the ipsilesional primary motor cortex has been associated with more severe post-stroke deficits. This study evaluated the therapeutic effects of transcranial magnetic stimulation (TMS) using theta burst stimulation (TBS) in reducing the inhibitory drive of the contralesional cortex.

This single center, prospective, randomized trial included adult patients with first ever ischemic stroke or intracerebral hemorrhage with paresis of the arm. Those subjects were assigned to receive a placebo or 10 daily sessions of transcranial magnetic stimulation using continuous theta-burst stimulation (cTBS) for two weeks. The stimulation sessions involved 40 seconds of cTBS with a biphasic TMS-induced current, with stimulation intensity set at 70% of the RMT. The primary outcome measure was the change in the Action Research Arm Test (ARAT) score from baseline at three months after stroke.

Data were analyzed for 28 patients in the cTBS group and 31 assigned to receive sham cTBS. The

improvements in ARAT scores from baseline to three months were 27.6 points in the active group and 18 points in the sham group ( $p=0.024$ ). In addition, Fugl-Myer scores were more improved in the treatment group than in the sham group ( $p=0.0196$ ).

**Conclusion:** This study of patients with an ischemic stroke found that treatment with continuous transcranial magnetic brain stimulation resulted in significant improved recovery of the upper arm function.

Vink, J., et al. Continuous Theta Burst Stimulation of The Contralesional Primary Motor Cortex for Promotion of Upper Limb Recovery after Stroke: A Randomized, Controlled Trial. *Stroke*. 2023, August; 54(8):1962-1971.

### FALL-RISK-INCREASING DRUGS AND FRACTURE RISK

Previous studies have identified so-called fall risk-increasing drugs (FRIDs), classes of medicines that increase the risk of falls. This population-based study quantified the association between exposure to these drugs and fracture risk in the elderly.

Data were obtained from a population-based data repository in Scotland, provided by the University of Dundee National Health Service (NHS) Tayside Health Informatics Centre. A case control analysis was made of individuals  $\geq 65$  years of age, with the exposures of interest including cardiovascular, psychotropic, and other fall-risk increasing drugs (FRIDs) included in the STOPP Fall list. During follow-up, cases were identified of individuals with an incident emergency hospital admission for a fracture. The risk of fracture was compared to exposure to one of the FRIDs of interest (diuretics, alpha blockers, drugs for overactive bladders, antiepileptics, opioids, antipsychotics, antidepressants, hypnotics, antihistamines, and anticholinergics).

Data were reviewed for a cohort of 246,535 adults, of whom 18,476 suffered an incident fracture. Patients  $\geq 75$  years of age had a 3.7-fold higher incidence than did those 65-74 years of age. The 90-day mortality rate was 10.3% for the entire group, and 12.4% among those  $\geq 75$  years of age. The relative risk of fracture increased with an increased number of FRIDs used. The highest absolute increased risk was found in those  $\geq 75$  years of age who were prescribed selective serotonin reuptake

inhibitors, tricyclic antidepressants, antipsychotics, or were prescribed three or more FRIDS.

**Conclusion:** This study of patients 65 years of age or older found that the greatest risk of fracture with drugs occurred in those 75 years of age or older who were prescribed antidepressants, antipsychotics or three or more of the “fall risk drugs”.

Hauff, J., et al. Single and Combined Use of Fall-Risk Increasing Drugs and Fracture Risk: A Population-Based, Case-Control Study. *Age Ageing*. 2023 June 1;52(6): 1-9.

### HIGH INTENSITY INTERVAL TRAINING FOR HEART TRANSPLANT PATIENTS

Previous studies have shown that peak oxygen consumption (VO<sub>2</sub>peak) is reduced in heart transplant patients (HTPs). High-intensity interval training (HIT) in non-HTPs has been found to be more effective than moderate-intensity continuous training for improving important aspects of heart function. This study investigated the effects of HIT on the structural and functional cardiovascular health of HTPs.

Within 13 weeks of a heart transplant, 81 recipients were randomly assigned to receive nine months of either supervised HIT or moderate-intensity continuous training (MICT). The HIT consisted of four, four-minute intervals of exercise at 85% to 95% of peak effort, separated by three minutes of active recovery at 60% to 70% of their peak effort. The MICT group received 25 minutes of continuous exercise at 60-80% of the peak effort. The primary outcome measures were the changes in left ventricular global longitudinal strain (LV GLS), LV dimensions including interventricular septal thickness at end-diastole (IVSd), left ventricular posterior wall at end-diastole (LVPWd) left ventricular internal diameter at end-diastole (LVIDd) and end-diastole volume (EDV) as assessed by echocardiography.

Data were analyzed for 74 patients including 37 in the standard care group and 29 in the HIT group. The GLS and LV end-diastolic volume (LVEDV) improved more in the HIT group than in the controls (p=0.02 and p=0.03, respectively). A non-significant difference in the change in microcirculation was noted in favor of the HIT group (p=0.08).

**Conclusion:** This randomized, controlled study of heart transplant recipients found that high intensity

interval training was superior to traditional, moderate intensity continuous training for improving GLS and LVEDV heart function.

Rafique, M., et al. Effects of High Intensity Interval Training on Cardiac Remodeling, Function, and Coronary Microcirculation in *De Novo* Heart Transplant Patients: A Substudy of the HITTS Randomized, Controlled Trial. *BMJ Open Sport Exer Med*. 2023 Jul 9;9(3):e001331. doi: 10.1136/bmjsem-2022-001331.

### BONE HEALTH IN ELITE RUNNERS

Weight bearing activity is known to contribute to bone health. However, excessive exercise, combined with restricted energy intake, has been shown to result in low energy availability (LEA), disturbed hormonal levels, reduced body fat, and increased bone stress injuries. This study compared the bone mineral density (BMD) of elite runners with that of an inactive control group.

Data for this study were obtained from a large study of Norwegian female, elite long-distance runners. Data collection included age, height, weight, training data, fat mass, hormone levels, and low energy availability (LEA). The primary outcome variables, BMD and body composition, were measured at the lumbar spine (L1-L4), proximal femur, and total body. Risk of LEA was assessed using the LEAF-Q.

The median and mean weekly running distances were 120 km (110-120) and 118 km (±19). Seven of the runners (47%) were classified as being at risk of LEA (LEAF-Q score of over eight) compared to two of the controls (13%). The bone density measurements were significantly higher in the dual proximal femur and total body in the runners, while the lumbar spine scores were similar between groups. Runners showed significantly lower levels of estradiol and luteinizing hormone than did controls. In runners, a positive correlation was found between estradiol and dual proximal femur BMD, with no such association with lumbar spine or total body BMD.

**Conclusion:** This study found that female, elite, long distance runners had significantly higher bone mineral density scores in the proximal femur and total body compared with age matched inactive controls.

Kyte, K., et al. Bone Health in Norwegian Female Elite Runners: A Cross-Sectional, Controlled Study.

*BMJ Open Sp Ex Med*. 2023, February 22;9(1):e001472.

### ELDERLY PATIENTS WITH ACUTE ISCHEMIC STROKE ONE YEAR AFTER THROMBECTOMY

Clinical trials have demonstrated the effectiveness of mechanical thrombectomy for the treatment of acute ischemic stroke (AIS). However, the very old are under-represented in many of these studies. This study was designed to better understand the effect of thrombectomy as a treatment for AIS among patients > 80 years of age.

This retrospective cohort study included 18,506 patients with AIS, treated with mechanical thrombectomy between 2010 and 2018. The subjects were grouped by age, including <60 years, 60 to 69 years, 70 to 79 years, 80 to 84 years, 85 to 89 years, 90 to 94 years, and over 94 years. The main outcome variables included overall survival, degree of disability, and home care situation.

Of the 18,506 patients, 6,729 were ≥80 years of age. In-hospital deaths occurred in 2,426. The one-year mortality rate of this group who were treated with thrombectomy was 55.4% as compared to 19.3% in the general population of those >80 years of age. Compared to patients <80 years of age, patients ≥80 years had lower rates of no/slight disability (17.4% vs 41.0%) and had higher rates of moderate to severe disability (35.5% vs 33.2%; p<0.001) and mortality (47.2% vs 25.8%; p<0.001).

**Conclusion:** This study of patients ≥80 years of age found that, after post-stroke mechanical thrombectomy, more than half were dead and fewer than one-fifth were functionally independent at one year.

Beuker, C., et al. Association of Age with One-Year Outcome in Patients with Acute Ischemic Stroke Treated with Thrombectomy: Real-World Analysis in 18,506 Patients. *J Neurol Neurosurg Psychiatry*. 2023, August; 94(8): 631-637.

### OREXIN RECEPTOR 2 AGONIST FOR NARCOLEPSY

Narcolepsy is a rare disorder of hypersomnolence, characterized by excessive daytime sleepiness. Low to absent orexin levels in the cerebrospinal fluid support a diagnosis of narcolepsy type 1. Orexins act through two G-protein-

coupled receptors, orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R), both of which are widely distributed in the brain. This study assessed the efficacy of a highly selective oral OX2R agonist that crosses the blood-brain barrier.

The TAK-994-1501 trial recruited patients with confirmed narcolepsy type 1 and randomized them to receive TAK-994 30 mg, 90 mg, 180 mg, or placebo. The primary endpoint was the change from baseline to week eight in average sleep latency on the 40-minute maintenance of wakefulness test (MWT), a measure of ability to stay awake under soporific conditions.

A total of 43 patients completed the trial. The least-squares mean changes to week eight in average sleep latency on the MWT were 23.9 minutes in the 30-mg group, 27.4 minutes in the 90-mg group, 32.6 minutes in the 180-mg group, and -2.5 minutes in the placebo group (difference vs. placebo,  $p < 0.001$  for all comparisons). Weekly incidences of cataplexy at week eight were more improved compared to placebo. The differences between the placebo and treatment groups in change from baseline in Epworth Sleepiness Scale scores were significantly better than the placebo group for all doses of the trail medication ( $p < 0.001$ ).

**Conclusion:** This randomized, controlled trial of patients with type I narcolepsy found that treatment with an orexin receptor 2 agonist could significantly improve sleep scores.

Dauvilliers, Y., et al. Oral Orexin Receptor 2 Agonist in Narcolepsy Type 1. *N Eng J Med.* 2023, July 17; 389: 309-321.

### INTRATHECAL OPIOIDS DURING CORONARY ARTERY BYPASS SURGERY

The intrathecal route of opioid administration has been well-established within the fields of anesthesia and pain management, primarily due to its ability to bypass the blood-brain barrier, requiring a lower dose to induce analgesic effects. This review article summarized the research concerning the efficacy of intrathecal opioids during cardiac bypass surgery.

A literature review was completed for studies of intrathecal opioid use in patients undergoing coronary artery bypass surgery, with outcomes including time to extubation, pain scores, postoperative analgesia, and length of stay. After the literature review, 28 studies reporting data from

4,000 patients were included in the meta-analysis. In 21 studies, with 988 patients, the time to extubation for the intrathecal opioid group was 3.51 hours compared to 4.76 hours for the control group ( $p = 0.04$ ). Length of stay in the ICU was reported in 13 studies with 3,057 patients, with no significant difference found between the control and treatment groups. Hospital length of stay was reported in 14 studies with 3,725 patients, demonstrating no significant change in hospital length of stay. Pain scores at one hour and 24 hours after surgery were found to be lower in the intrathecal opioid group than in the placebo group ( $p < 0.001$  and  $p = 0.001$ , respectively). Studies reviewing postoperative analgesic requirements revealed that those in the intrathecal opiate group had less postoperative analgesia for pain at 24 hours and 48 hours than did the placebo group ( $p < 0.001$  for both).

**Conclusion:** This literature review of studies involving patients undergoing coronary artery bypass grafting found that the use of intrathecal opioids during surgery reduced the time to extubation and improved postoperative analgesia requirements for pain control.

Young, E., et al. Do Intrathecal Opioids Improve Surgical Outcomes after Coronary Artery Bypass Grafting? A Systematic Review and Analysis. *Pain Physician.* 2023, Jul;26(4):319-326.

### UNTREATED UNRUPTURED ANEURYSMS

Subarachnoid hemorrhage (SAH), resulting from rupture of intracranial aneurysms, is a condition associated with increased mortality and morbidity. This study investigated the incidence of SAH and growth of unruptured intracranial aneurysms (UIAs) to better understand the risk factors for growth and rupture.

The subjects were consecutive patients, referred to the senior author between January 2008 and January 2021, who had been found to have a UIA. Data were collected including demographics, presenting complaint, medical comorbidities, smoking status, and description of the location and size and morphology of the aneurysm.

Data were recorded describing 445 aneurysms in 274 patients. Of these, 70.1% presented with an unrelated condition. Growth was detected in 27 UIAs during the study period, representing a 1.2% annual risk of growth. The overall annual risk

of rupture was 0.46%. In a multivariate logistic regression analysis, predictors of growth or rupture were size  $> 7$ mm compared to  $< 3$ mm ( $p < 0.0005$ ), current smokers compared to never smokers ( $p = 0.012$ ),  $< 50$  years of age ( $p = 0.002$ ), and hypertension ( $p = 0.027$ ).

**Conclusion:** This study of unruptured aneurysms found that the risk of rupture or growth was increased among those with a diameter of greater than 7 millimeters, current smokers, less than 50 years of age and hypertension.

Spencer, R., et al. Unruptured Untreated Intracranial Aneurysms: A Retrospective Analysis of Outcomes of 445 Aneurysms Managed Conservatively. *Br J Neurosurg.* 2023, May 5; 1-9 doi.org/10.1080/02688697.2023.2207646.

### MITOCHONDRIAL DNA AND KNEE CARTILAGE DAMAGE

Recent evidence suggests that mitochondrial dysfunction is an acute response of chondrocytes to mechanical injury, resulting in several processes that lead to the development of post-traumatic osteoarthritis (PTOA). This study was designed to determine whether injured chondrocytes release mitochondrial DNA (mtDNA), to measure synovial fluid mtDNA in vivo and naturally occurring models of cartilage injury, and to investigate the effect of mitoprotection on mtDNA release.

Measurements were made of mtDNA release using four models of OA. These included, in vitro chondrocyte stimulation, ex vivo cartilage impact injury, in vivo cartilage impact injury and naturally occurring intra-articular fracture cases using racehorse data. In the in vitro model equine chondrocytes were cultured either with (IL-1b) or without (NS) a sublethal dose of IL-1b for 12 hours. This was followed by measurement of mtDNA and nuclear DNA (nDNA). In the in vivo model, after a surgically delivered cartilage injury, one group was treated with an intraarticular injection of the mitoprotective peptide SS-31, delivered one hour after injury. The mtDNA was then quantified. In the naturally occurring cases, clinical data (radiographs, arthroscopic video footage) were scored for criteria associated with degenerative joint disease.



(Continued from page 2)

\*Clara Yuh, D.O.  
Michael Bazzi, D.O.  
Richard Catabona, D.O.  
Edward Chang, D.O.  
David Ho, D.O.  
Clara Gannon, MS2  
Kevin Robinson, BS  
Eric Nguyen, OMS-IV  
Justin Tram, BA  
UC Irvine, Irvine, CA

\*Gurtej Bajaj, M.D.  
Tejas Shah, M.D.  
Peter Spurrell, M.D.  
David Weinberg, M.D.  
UPenn, Philadelphia, PA

\*Martin Laquerre, M.D.  
Ziyi Chen, M.D.  
Joshua Kaseff, M.D.  
Imran Murtuza, M.D.  
Chiamaka Ukoha, M.D.  
UT SW Med Ctr. Dallas, TX

\*Sandra de Mel, M.D.  
Robin Mata, D.O.  
David Alwin, M.D.  
Univ. of Miami/JHS, Miami, FL

\*Joshua Wilson, M.D.  
Jaimie Hearn, M.D.  
Garrett Wahl, M.D.  
Univ. Of Washington, Seattle, WA

**Executive Editor Emeritus**  
Donald F. Langenbeck, Jr., M.D.

**Subscription Manager**  
Michael P. Burke, M.S.

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In both the inflammatory and mechanical/impact studies, mtDNA was released by chondrocytes, and returned to normal after the stimulation was withdrawn. In both the experimental/surgical and natural occurring impact conditions a significant rise in extracellular mtDNA was found as compared to controls. In the naturally occurring model, using racehorse data, a strong positive correlation was found between the degree of cartilage damage and mtDNA concentration ( $p= 0.0001$ ). Finally, impact-induced mtDNA release was mitigated by microprotective treatment with SS-31.

**Conclusion:** This animal study demonstrates that chondrocytes release mtDNA in response to mechanical and inflammatory stress, that changes in synovial fluid mtDNA are detectable following articular injury, and that these can be mitigated by a mitoprotective peptide.

Seewald, L., et al. Synovial Fluid Mitochondrial DNA Concentration Reflects the Degree of Cartilage Damage After Naturally Occurring Articular Injury. **Osteoarthritis Cartilage.** 2023, August; 31(8): 1056-1065.

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