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CAROTID FILTER FOR ATRIAL FIBRILLATION

It is well understood that patients with atrial fibrillation (AF) who are not treated with oral anticoagulants have an elevated risk of stroke. However, among high-risk patients, the annual stroke risk remains excessive despite taking oral anticoagulants. Approximately 80% of strokes in patients with AF are caused by emboli-produced occlusions of the main branches of the carotid arteries. This study assessed the efficacy of common carotid artery filters designed to capture these emboli.

The Carotid Artery Implant for Trapping Upstream Emboli for Preventing Stroke in Atrial Fibrillation Patients (CAPTURE) is a multi-center feasibility study of the CCA filter. Subjects were patients with persistent or permanent AF, unsuitable for oral anticoagulants, and CHA_2DS_2-VASc>2. After filter placement, the participants received aspirin/ clopidogrel daily for three months, and then aspirin 81 to 100 mg for the duration of the study. The primary safety endpoint was device- or procedure-related, major adverse events. The primary feasibility endpoint was the absence of device-related, major adverse events, along with proper filter positioning.

Subjects were 25 patients with a mean age of 71.3 years, 23 of whom underwent bilateral filter placement. At 30 days, the primary safety endpoint was achieved by all subjects. The primary feasibility endpoint was achieved in 23 of the 25 patients. Of the 47 implants that were properly positioned at the end of the procedure, 100% remained properly positioned at up to 12 months follow-up. There were six occurrences of thrombi in the CCA filter, though no interruption of blood flow was noted.

Conclusion: This study of patients with atrial fibrillation found that a percutaneous permanent carotid filter is feasible and safe.

Reddy, V., et al. A Percutaneous Permanent Carotid Filter for Stroke Prevention in Atrial Fibrillation: The CAPTURE Trial. **J Amer College Cardiol** (2019), doi: https:// doi.org/10.1016/j.jacc.2019.04.035.

TARGETING FILAMIN A FOR ATHEROSCLEROSIS

Atherosclerosis is a progressive inflammatory disease in which monocyte-derived macrophages are dominant. The mechanisms behind the function of macrophages within atherosclerotic plaques is not completely understood. A large actin-binding protein *Flna* (filamin A) assists in the integration of cell architecture and signaling pathways important for cell function. Recent observations have implicated *Flna* as a potentially important protein in atherogenic processes. This animal study investigated the role of *Flna* in macrophages involved in the atherosclerotic process.

Atherosclerotic plaques were harvested from carotid endarterectomies, in order to measure the expression of *Flna*. In a separate animal study, a mouse model was produced, deficient in macrophage *Flna*. The mice expressing *Flna* (Flnao/fl) were compared to those lacking *Flna* (Flnao/fl/LC). All animals were fed a high-fat diet for 20 weeks, with their aortas then harvested for comparison.

In the carotid arteries harvested at endarterectomy, a higher number of intimal macrophages were observed in advanced plaques than in intermediate plaques ($p<0.05$). Compared to the *Flna* (*Flnao/fl*) mice, the size of the atherosclerotic plaques in the *Flna* (*Flnao/fl/LC*) subjects was reduced by 55% ($p<0.001$). Treatment of Flnao/fl macrophages with the calpain inhibitor, calpeptin, reduced the production of *Flna* by 64 % ($p<0.01$). Treatment with calpeptin reduced aortic atherosclerotic plaque size by 49% ($P<0.05$).

Conclusion: This study found that inactivating or inhibiting the actin binding protein *Flna* reduces atherosclerosis in mice, suggesting a potential target for the treatment of atherosclerosis.

Bandaru, S., et al. Targeting Filamin A Reduces Macrophage Activity and Atherosclerosis. **Circulation**. 2019, July 2; 140(1):67-79.

HIGH-SENSITIVITY C-REACTIVE PROTEIN AND CAROTID PLAQUE

C-reactive protein (CRP) is widely accepted as a predictive factor for the risk of cardiovascular diseases. This study assessed whether CRP is associated with carotid artery plaque (CAP).

This retrospective cohort study included 8,229 community dwelling, Chinese adults, 65 years of age or older, recruited between January of 2013 and October of 2018. At baseline, high-sensitivity CRP (hsCRP) was measured and ultrasound imaging was performed to assess CAP. Ultrasound was performed annually for five years.

Other measurements included body weight and height, in order to determine body mass index, and lab values for alanine transferase, aspartate transferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, direct bilirubin, blood urea nitrogen, creatinine, uric acid, fasting blood glucose, total cholesterol, triglycerides, HDL (high-density lipoprotein) cholesterol and LDL (low-density lipoprotein) cholesterol.

An elevated baseline hsCRP was found to be associated with an increased risk of CAP. Each unit of increase in baseline hsCRP was associated with a 17% greater risk of CAP. In addition, each unit of increase in baseline hsCRP was associated with a 10% higher likelihood of developing incident CAP.

Conclusion: This community-based study found that high baseline CRP concentration is associated with

a high prevalence and incidence of CAP, after adjusting for a series of potential compounders.

Xu, R., et al. High-Sensitivity CRP (C-Reactive Protein) Is Associated with Incident Carotid Artery Plaque in Chinese Aged Adults. **Stroke.** 2019, July; 50: 1655-1660.

HEAD INJURIES IN MALE SOCCER AFTER A RULE CHANGE

A unique feature of football (soccer) is the intentional use of the head to strike the ball. Based on an analysis of head injuries during World Cup play, the International Football Association Board altered the rules in 2006 such that direct and deliberate elbows to the head were punished with a red card (eviction from the match). This study assessed the effects of this rule change on the incidence of head injuries.

This retrospective analysis was made of head injuries recorded in the first German Male Bundesliga during the seasons 2000/01–2012/13. Injuries were recorded and published in the German football magazine *Kicker Sportmagazin* which is published twice weekly with one journalist being responsible for one club and having daily contact with the club. The severity of injuries was determined by the time lost from practice or competition.

During the observation periods, 356 head injuries were recorded, with an incidence rate of 2.22 per 1000 match hours. Compared to the rate of head injuries before the rule change, the rate of head injuries was reduced by 29%, including a 29% reduction in concussions and a 16% reduction in facial fractures.

Conclusion: This study of German male soccer players found that, after a rule change calling for the ejection of players who inflicted direct and deliberate elbows to the opponent's head, there was a 29% reduction in head injuries during match play.

Beaudouin, F., et al. Head Injuries in Professional Male Football (Soccer) Over 13 Years: 29% Lower Incidence Rates after a Rule Change (Red Card). **Br J Sports Med**. 2019, August; 53:948–952.

REPETITVE HEAD IMPACTS IN SOCCER

Repetitive head impacts (RHI) are defined as mild impacts that do not result in a known or diagnosed concussion. While the long-term effects of RHIs have been studied, the short- to medium-term effects have been less often studied and less well understood. This study was designed to determine the effect of RHI on clinical assessments across one season.

Subjects were collegiate football (FB) and women soccer (WSOC) players. All were tested two weeks before the start of the competitive season, and within one week after the end of the season. The ImPACT and several other functional and cognitive evaluations were completed. Exposure to RHI was quantified using the head impact telemetry system for FB players and the Smart Impact Monitor for WSOC players. Forces were measured by an accelerometer, inserted into individual helmets. Data were transmitted wirelessly to determine real-time head impact kinematics. Data from the accelerometers were compared with changes in cognitive and functional scores.

In the WSOC cohort, associations were found between increased RHI exposure and impaired eye movements and saccades and poorer visual memory ($p=0.002$) and tandem gait (TG) ($p=0.029$). In the FB cohort, greater RHI was associated with poorer performance on the King-Devick (KD) measurement of speed for rapid number naming and reading ($p=0.013$). The number of impacts greater than 98 g made significant and unique contributions to the reduction of scores on visual memory, TG and KD. Overall, however, RHIs did not produce clinically meaningful changes in scores on a concussion assessment battery.

Conclusion: This study of high-level soccer players does not provide evidence that repetitive head impacts result in clinically meaningful changes in neurologic health.

Caccese, J., et al. Effects of Repetitive Head Impacts on a Concussion Assessment Battery. **Med Sci Sports Exerc.** 2019, July; 51(7): 1355-1361.

SOCCER HEADGEAR AND CONCUSSION IN ADOLESCENCE

Concussion injuries comprise eight to 13 percent of all sports injuries sustained in high school. This study was designed to determine whether players wearing headgear have a lower number of concussions than do those not wearing headgear.

High school soccer teams were invited, with participant schools randomized to a headgear (HG) group or a no-headgear (NoHG) group. Injuries and exposures were recorded for each player over a single season. Those in the HG group were allowed to individually choose a headgear model from those meeting the ASTM testing standards. Licensed trainers working with these teams were responsible for in-season data collection and determining the onset mechanism injury characteristics and diagnosis of all sports-related injuries.

Data were collected for 2,766 participants. Over the season, 130 sports-related concussions were recorded. The rate of sports-related concussions did not differ significantly between the HG group (4.4%) and the NoHG group (4.1%). In addition, no significant difference between the two groups was noted in the number of days with concussion symptoms.

Conclusion: This study of adolescent soccer players did not find that headgear can reduce the risk of concussion.

McGuine, T., et al. Does Soccer Headgear Reduce the Incidence of Sport Related Concussion? A Cluster, Randomized, Controlled Trial of Adolescent Athletes. **Br J Sports Med**. 2019; 0: 1-6.

TREATMENT OF MIGRAINE IN THE EMERGENCY DEPARTMENT

In recent years, a number of non-opioid medications have been found to be effective for the treatment of migraines in the emergency department (ED), including prochlorperazine, metoclopramide and ketorolac. This study assessed whether the treatment of migraine patients in the ED has changed in recent years.

This retrospective hospital study included data from four New Jersey suburban hospitals concerning patients treated in the ED for migraine from 1990 to 2014. Data retrieved included medications given in the ED, the use of IV fluids and prescriptions given at discharge. Rates of ED revisit within 72 hours were determined for each year of the study. Results for the year 1999-2000 were compared with those for the year 2014.

Of the 2,824,710 ER visits, 8,046 (0.28%) were for migraine. Treatments which were found to have increased between 1999 and 2014 included IV fluids, prochlorperazine/ metoclopramide, ketorolac and dexamethasone, by 74%, 58%, 34% and 22%, respectively. Narcotic prescriptions at discharge and parenteral narcotics in the ED decreased by 56% and 22%, respectively. The revisit rates within 72 hours decreased from 12% in 1990 to four percent in 2014.

Conclusion: The use of non-narcotic medications to treat migraines has increased from 1999 to 2014. Additionally, the revisit rate for migraines has decreased significantly during the same time period.

Ruzek M., et al. ED Treatment of Migraine Patients has Changed. **Am J Emerg Med.** 2019, June; 37(6): 1069-1072.

VERY EARLY INITIATION DURING STROKE REHABILITATION

In the EXCITE Stroke Trial, constraint-induced movement therapy, initiated three to nine months after stroke was found to significantly improve function. Subsequent studies have suggested that recovery could be impeded if therapy was introduced too early or at too great an intensity. This animal study examined how modifications of the time of initiation could impact recovery after a severe cortical stroke.

Subjects were 75 adult rats with stroke induction at the caudal forelimb area (CFA) and rostral forelimb area (RFA). The subjects were divided into six groups to perform daily interventions; control, n = 16; forced use (immediate), n = 9; forced use (day 1), n = 8; forced use (day 4), n = 9; forced non-use (day 4), n = 9 and forced use + skilled forelimb training (SFT) (day 4), n = 10. Tests of behavior and motor function were performed five days per week for three weeks, beginning 24 days post-stroke. At three days after the final behavioral testing, the animals received an injection of Fast Blue into the dorsal column and retro-beads into the contralateral side of gray matter, to assess spinal projection neurons and lesion volume.

Forced use, beginning one or four days after stroke, resulted in significant functional improvement. However, immediate forced use resulted in no functional improvement, with a non-significant tendency towards greater disuse of the affected limb on day 24. Combining forced use and skilled forelimb training improved functional recovery on multiple tasks significantly more than did simple forced use alone. The tracer study found that immediate forced use and combination training, increased corticospinal projections from the contralesional and ipsilesional motor cortex, respectively.

Conclusion: This animal stroke study indicates that enhanced skilled forelimb training improves the restoration of corticospinal projections and boosts rehabilitation-induced functional recovery. However, the initiation of training too early reduced the benefits of rehabilitation, despite increased corticospinal projections.

Okabe, N., et al. Very Early Initiation Reduces Benefits of Post-Stroke Rehabilitation Despite Increased Corticospinal Projections. **Neurorehabil Neural Repair**. 2019:33 (7): 538-552.

SUBSYNDROME DELIRIUM AFTER ISCHEMIC STROKE

After a stroke, patients with delirium have been found to have increased rates of institutionalization and mortality and worse functional outcome. Subsyndromal delirium (SSD), an intermediate state between delirium and normal cognition, refers to delirious symptoms which do not meet the strict criteria for delirium. This study explored the association between SSD and outcomes of patients with acute stroke.

This prospective, observational study was completed between 2014 and 2016 in Kraków, Poland. Subjects were adult patients with acute stroke, admitted within 48 hours of symptom onset. Those with intracerebral hemorrhage, or who could not be assessed with the Brief Confusion Assessment Method (BCAM) were excluded. Patients were screened daily for symptoms of delirium during the first seven days of hospitalization, using the BCAM for verbal patients, and the Intensive Care Units version for non-verbal patients. Using these scores, the patients were placed in one of three categories; delirium, SSD and no delirium/no SSD (ND/NSSD) groups.

Of the 564 patients, SSD was found in 10.3%, delirium in 23.4% and ND/NSSD in 66.3%. The risk of unfavorable outcome at three and 12 months was 22.2 % and 21.8% of the ND/NSSD group, in 60.4% and 56.4% of the SSD group and 82.1% and 81.3% of the delirium group ($p<0.01$). Mortality at 12 months was 9.9% in the ND/NSSD group, 21.8%

in the SSD group and 47.2% in the delirium group (p<0.01).

Conclusion: This study of patients with acute stroke found that subsyndromal delirium is independently associated with unfavorable outcome after stroke.

Klimiec-Moskal, E., et al. Subsyndromal Delirium Is Associated with Poor Functional Outcome after Ischemic Stroke. **Euro J Neurol.** 2019; 26: 927-934.

LONG DOSE, INTENSIVE THERAPY FOR UPPER LIMB FUNCTIONAL GAINS AFTER STROKE

Constraint-induced movement therapy has been shown to be an effective treatment for mild/moderate stroke. However, studies of more severe stroke have reported less clinical efficacy. This study tested whether the duration of therapy is significantly related to the degree of recovery in patients with moderate/ severe stroke.

Subjects were patients with single, unilateral stroke, with at least trace muscle contraction of the affected wrist extensors. Therapy was implemented for five hours per day, five days per week, for 12 weeks. Assistive technology (functional electrical stimulation and robot assist) was included in the training for 1.5 hours per session, including functional electrical stimulation for wrist/hand muscles (distal focus), functional electrical stimulation and robotics for shoulder/ elbow muscles (proximal focus), and a combination of the two (whole arm). Subjects were assessed using the Fugl-Meyer Assessment (FMA).

No significant differences were found between the treatment groups in functional outcome scores. Combining all treatment groups, compared to a control group, significant FMA gains were found at mid-treatment, post-treatment and follow-up (p<0.0001 for all comparisons). Significant, additional improvement was found with treatment extended from 150 to 300 hours (p<0.0001). Significant improvements were maintained at long-term follow-up.

Conclusion: This study of patients with severe to moderate, chronic stroke found that 150 hours of therapy are necessary to achieve significant recovery, with treatment extended to 300 hours resulting in additional improvement.

Daly, J., et al. Long-Dose Intensive Therapy is Necessary for Strong, Clinically Significant, Upper Limb Functional Gains and Retained Gains in Severe/Moderate, Chronic Stroke. **Neurorehab Neural Repair.** 2019, July; 33 (7): 523-537.

ERYTHROPOIETIN AND TRAUMATIC BRAIN INJURY

Several randomized, controlled trials (RCTs) and prospective studies have assessed the application of erythropoietin (EPO) to treat diseases associated with neuroinflammation and apoptosis. The use of EPO for the treatment of brain injury has yielded conflicting results. This literature review and meta-analysis was designed to better understand the efficacy of EPO for the treatment of patients with traumatic brain injury (TBI).

A literature review was completed for studies evaluating the efficacy of erythropoietin as a treatment for TBI. From the review, six, randomized, controlled trials were chosen, with a total of 1,041 patients. The data were reviewed for the effect of EPO on mortality, neurologic outcome, death and DVT as a complication.

Compared with placebo, EPO administration was associated with decreased mortality, with a relative risk of 0.68 (p=0.02). A favorable neurologic outcome, defined as a Glasgow Outcome Scale score of four to five, was found in 54.5% of those who received EPO, compared to 49.1% of the control group. In surviving patients, unfavorable outcome was noted in 34.9% of the EPO treated group and 35.4% of the untreated group. A DVT was found in 11.8% of the EPO treated group and 14.1% of the untreated group.

Conclusion: This literature review and meta-analysis found that the use of EPO as a treatment for patients with traumatic brain injury was associated with lower mortality and an increase in favorable outcome.

Lee, J., et al. Efficacy and Safety of Erythropoietin in Patients with Traumatic Brain Injury: A Systematic Review and Meta-analysis. **Am J Emerg Med.** 2019, July; 37: 1101-1107.

ORTHOSTATIC HYPOTENSION AND RECURRENT STROKE

Orthostatic hypotension (OH) is associated with an increased stroke risk in the general population. This study assessed whether OH after lacunar stroke is associated with an increased risk of recurrent stroke.

This retrospective cohort study used the Secondary Prevention of Small Subcortical Strokes (SPS3) patient cohort, consisting of patients with symptomatic lacunar infarcts within the preceding six months. Participants had both sitting and standing blood pressures (BPs) measured at baseline and at follow-up. The patients were grouped according to the presence of OH. Orthostatic hypotension was defined as either a decline in systolic BP of at least 20 mmHg or a decline in diastolic BP of at least 10 mmHg with posture change from sitting to standing. The primary outcome was recurrent ischemic stroke. The mean follow-up was 3.2 years.

Of the 2275 enrollees, 39% (881/2275) had OH at one or more follow-up appointments. Of these 41% had orthostatic symptoms corresponding with these blood pressure drops. In the final adjusted model, those with OH had a 1.8 times higher risk of recurrent stroke than did those without OH. In addition, those with OH had a 1.9 times higher risk of all-cause death than did those without OH. No significant associations were found between OH and hemorrhagic stroke or myocardial infarction.

Conclusion: This retrospective cohort study of patients with lacunar stroke demonstrates that orthostatic hypotension is associated with an increased risk of recurrent stroke, and death.

Mehta, T., et al. Effect of Postural Hypotension on Recurrent Stroke: Secondary Prevention of Small Subcortical Strokes (SPS3) Study. **J Stroke Cerebrovasc Dis**. https:// doi.org/10.1016/ j.jstrokecerebrovasdis.2019.04.009.

TESTOSTERONE ADMINISTRATION AFTER TRAUMATIC BRAIN INJURY

After a traumatic brain injury (TBI), initial pathophysiological changes resulting from primary mechanical damage can produce secondary effects, including progressive neurodegeneration. In experimental TBI, mitochondrial dysfunction has commonly been described as a source of cellular metabolic crisis. As previous research has shown potential neuroprotective effects of

testosterone, this animal study explored the effect of testosterone on mitochondrial function.

Thirty mice underwent a controlled cortical impact (CCI). The animals were randomized to receive daily injections of a placebo or testosterone cypionate 15 mg/kg per day for 10 days after the head trauma. At 24 hours after the CCI injury, the subjects were assessed with the modified Neurological Severity Score. At 10 days, the ipsilateral cortex of each subject was collected for analysis.

After CCI, the control group was found to have increased Ca2+ induced mitochondrial swelling after the addition of metabolic substrates [pyruvate, malate, glutamate, succinate and adenosine diphosphate (PMGSA)]. The reduction in Ca2+ efflux post-injury was associated with impaired mitochondrial membrane potential formation/dissipation and decreased mitochondrial adenosine triphosphate-synthase coupling efficiency. Evidence of mitochondrial uncoupling was observed, with an increase in H2O2 production, after the CCI injury. Testosterone administration significantly reduced these neuroenergetic alterations, and produced a downregulation of mitochondrial apoptotic signals.

Conclusion: This animal study suggests that testosterone administration after a severe traumatic brain injury can improve mitochondrial calcium extrusion and mitochondrial adenosine triphosphate synthesis efficiency, down-regulating drivers of neurodegeneration.

Carteri, R., et al. Testosterone Administration after Traumatic Brain Injury Reduces Mitochondrial Dysfunction and Neurodegeneration. **J Neurotrauma.** 2019; 36(14): 2246-2259.

ANTERIOR CRUCIATE LIGAMENT AND MENISCUS REPAIRS AND RISK OF KNEE REPLACEMENT

Previous studies have suggested that injuries to the anterior cruciate ligament (ACL) as well as injuries to the meniscus, increase the risk of developing osteoarthritis (OA) of the knee. This study was designed to quantify the risk of undergoing a total knee replacement (TKR) among patients with a history of ACL repair or meniscal injury repair.

Within the United Kingdom Clinical Practice Research Datalink (CPRD), ACL, meniscal injury and joint replacement are coded and recorded. A matched case-control study was undertaken of all primary TKRs in the United Kingdom, recorded in the CPRD, performed between 1991 and 2011. Each primary TKR was matched with two controls who had no history of ACL repair.

Subjects included 49,723 individuals with TKR and 104,353 controls. Compared to those without a history of ACL repair, the adjusted risk of undergoing a TKR within 20 years was significantly greater among those with an ACL repair (odds ratio (OR) 6.96). Further, compared to those without a history of meniscal injury repair, the adjusted risk of TKR within 20 years was significantly greater among those with a meniscal repair (OR 15.24). The adjusted OR for TKR in individuals with both a recorded ACL repair and meniscal injury repair compared with those with only an ACL repair was 4.19.

Conclusion: This matched case–control study of all TKRs performed in the UK between 1990 and 2011 found that those with a history of ACL injury have a sevenfold increased odds of a subsequent TKR.

Khan, T., et al. ACL and Meniscal Injuries Increase the Risk of Primary Total Knee Replacement for Osteoarthritis: A Matched Case–Control Study Using the Clinical Practice Research Datalink (CPRD). **Br J Sports Med**. 2019, August; 53 (15):965-968.

PRIOR ACL SURGERY AND OUTCOME OF KNEE REPLACEMENT

Studies have suggested that anterior cruciate ligament (ACL) injury and surgery may accelerate osteoarthritis (OA), particularly when associated with meniscal damage. Patients with a history of ACL repair undergo total knee arthroplasty (TKA) at a higher rate than do patients without such a history. Therefore, this study compared the clinical outcomes of patients with a TKA with a history of ACL repair to those without previous ACL repair.

A systematic review of the medical literature was completed of studies published through November 2018. Eligible studies compared outcomes of patients undergoing TKA with and without a history of ACL repair. The review identified five studies including 318 patients with a history of ACL repair and 455 matched controls. The mean time between the ACL repair and TKA was 21.8 years. Postoperative subjective outcome scores, as measured by the Knee Society Score, did not differ significantly between the two groups. In addition, no significant difference was noted between groups in pain and function as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. The risk of repeat surgery was slightly higher for the ACL group.

Conclusion: This literature review of patients with total knee replacement found that those with a history of ACL repair had outcomes similar to those without such a history.

Chaudhry, Z., et al. Does Prior Anterior Cruciate Ligament Reconstruction affect Outcomes of Subsequent Total Knee Arthroplasty? A Systematic Review. **Orthop J Sports Med.** 2019, July; 7 (7).

ELECTRICAL STIMULATION AND ARM FUNCTION AFTER STROKE

Several types of electrical stimulation have been used to assist motor recovery in patients with stroke. This meta-analysis examined the current evidence regarding the efficacy of electrical stimulation (e-stim) for arm function recovery after stroke.

A literature search was conducted for randomized, controlled trials reporting effects of e-stim on arm function after stroke. Primary outcome measures included upper extremity Fugl-Meyer Assessment (FMA) scores, pairing three types of electrical stimulation (EMG–triggered, cyclic or sensory electrical stimulation).

From the literature search, 48, randomized controlled trials were identified and included in the analysis. The analysis revealed that FMA scores were better for patients in the e-stim groups than for those in the placebo groups immediately after therapy ($p<0.00001$) and at follow-up ($p<0.00001$). A comparison between EMG triggered, cyclic and sensory electrical stimulation did not reveal significant differences in outcomes.

Conclusion: This meta-analysis of patients with stroke found that those treated with electrical stimulation had better improvement in arm function than did those treated with placebo.

Yang, J., et al. Effectiveness of Electrical Stimulation Therapy in Improving Arm Function after Stroke: A Systematic Review and a Meta-analysis of Randomized, Controlled Trials. **Clin Rehab.** 2019, August; 33 (8): 1286-1297.

ARGININE-STIMULATED COPEPTIN FOR DIAGNOSIS OF DIABETES INCIPITUS

For decades, the gold standard for diagnosing diabetes insipidus (DI) was the indirect water deprivation test. Arginine is known to stimulate the anterior pituitary gland to secrete various hormones, and is widely used to diagnose growth hormone deficiency. This study assessed whether arginine can also stimulate the posterior pituitary to release vasopressin and provide a simple, alternative test for the diagnosis of DI.

This prospective study included patients referred with polyuria or undergoing clinical care with a known diagnosis of central DI or primary polydipsia. All subjects underwent a standardized arginine infusion after an overnight fast of eight hours' duration and a fluid restriction of two hours' duration. The arginine was delivered over 30 minutes at 0.5 g/kg. At baseline and at 30, 45, 60, 90 and 120 minutes after the start of the arginine infusion, blood was drawn for copeptin measurement. The primary endpoint was the ability to discriminate between patients with central DI and those with primary polydipsia.

Subjects were 31 patients with primary polydipsia, and 12 with complete and nine with partial DI, as well as 20, healthy, adult controls and 42 child controls with short stature who were enrolled in a separate development cohort. In the pooled patient dataset, the median copeptin values for those with primary polydipsia doubled after arginine stimulation ($p<0.0001$). By contrast, copeptin concentrations in patients with DI increased only slightly after arginine stimulation. A copeptin cutoff of 3.8 pM/L at 60 minutes post-infusion had an accuracy of 93% for differentiating between DI and primary polydipsia.

Conclusion: This study suggests that arginine stimulated copeptin measurements may provide a simple and safe approach for diagnosing diabetes insipidus.

Winzeler, B., et al. Arginine Stimulated Copeptin Measurements in the Differential Diagnosis of Diabetes Insipidus: A Prospective, Diagnostic Study. **Lancet**. http://dx.doi.org/10.1016/S0140-6736(19)31255-3.

NICOTINE BITARTRATE AND FALLS IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a disabling neurodegenerative disease. In these patients, falls are often refractory to, and sometimes worsened by, levodopa. Nicotine bitartrate (NB), a direct agonist at central nervous system cholinergic-15 receptors, produces a higher-level selective stimulation of nicotine receptors. This study investigated whether NB can reduce falls and freezing of gait in patients with PD.

This randomized, placebo-controlled trial of adult patients with PD was completed in 12 centers in the United States. The participants were randomized to receive either NB or a placebo, four times per day for 10 weeks. All subjects began at a dosage of one mg every six hours at baseline, escalating upward at two-week intervals until reaching 24 mg per day for four weeks. Falls were measured on a five-point scale from no falls to falls more than once per day. Freezing of gait (FOG) and falls related to FOG were measured on a five-point scale from no FOG to frequent falls from FOG.

Data were analyzed for 30 patients in the treatment group and 27 in the placebo group. Fourteen of the 30 treatment patients reported a reduction in falls, as compared to three of 27 in the placebo group ($p=0.0043$). In addition, as compared to controls, the treatment group had a significantly greater reduction in FOG, with 12 of 30 patients in the treatment group, and four of 27 patients in the control group, reporting a reduction in FOG ($p= 0.0041$).

Conclusion: This study found that a nicotine receptor agonist, nicotine bitartrate, can reduce falls and freezing of gait in patients with PD.

Lieberman, A., et al. Nicotine Bitartrate Reduces Falls and Freezing of Gait in Parkinson Disease: A Reanalysis. **Frontiers Neurol.** 2019, May; 10: 424.

ALIROCUMAB TREATMENT AFTER ACUTE CORONARY SYNDROMES

Previous studies have shown that monoclonal antibodies that target PCSK9 produce substantial and sustained reductions in low-density lipoprotein cholesterol (LDL-C). Previous studies have shown that treatment with PCSK9 antibodies reduced nonfatal cardiovascular events in patients with high cardiovascular risk or stable atherosclerotic cardiovascular disease. The ODYSSEY OUTCOMES was designed to assess the efficacy of the PCSK9 human monoclonal antibody in patients with a recent acute coronary syndrome (ACS) who had elevated atherogenic lipoproteins, despite intensive statin therapy.

Subjects were patients 40 years of age or older, hospitalized with ACS, with LDL-C levels of $\geq$70 mg/dL or non-high-density lipoprotein cholesterol levels of $\geq$100 mg/dL or apolipoprotein B levels of $\geq$80 mg/dL, despite maximum treatment with statins. The subjects were randomly assigned to treatment with alirocumab, 75 mg, or a matching placebo, given by subcutaneous injection every two weeks. The primary end point was the composite of death caused by CHD, nonfatal myocardial infarction, ischemic stroke or unstable angina requiring hospitalization. The primary efficacy endpoint was the time to the first occurrence of a given endpoint, including composite of death caused by CHD, myocardial infarction, ischemic stroke or unstable angina.

A total of 18,924 patients in 57 countries were randomized. At a median 2.8 year follow up there were 334 deaths in the treatment group and 392 in the placebo group ($p=0.03$). The absolute risk reduction for death at four years was 1.1% with alirocumab treatment. The primary endpoint occurred in 9.5% of the treatment group and in 11.1% 0f the placebo group ($p<0.001$). The treatment effect was not evident until after the first year.

Conclusion: This study of patients with elevated lipids despite maximal statin therapy found that the addition of alirocumab is associated with reduced mortality.

Steg, P., et al. Effect of Alirocumab on Mortality after Acute Coronary Syndromes. An Analysis of the ODYSSEY OUTCOMES

Randomized, Clinical Trial. **Circulation.** 2019, July 9; 140(2): 103-112.

SLEEP DISTURBANCE AND CHRONIC PAIN

Chronic pain is often associated with a poor quality of life, negative affect and functional impairment. Many patients with chronic pain also report a sleep disturbance. This study examined direct and indirect pathways by which sleep disturbance may affect chronic pain intensity and functional status.

Subjects were 87 adults with chronic low back pain (CLBP) of at least three months' duration, without daily opioid analgesics. Sleep disturbance was assessed using the PROMIS sleep disturbance-short form 8a, assessing sleep quality, sleep depth and restoration associated with sleep. Subjects were also assessed using chronic pain intensity measures (the McGill Pain Questionnaire (MPQ)-Short Form, including a visual analogue scale (VAS) of pain intensity, and assessments of sensory (MPQ-sensory) and affective (MPQ-affective) quality of pain, psychosocial measures, and functional measures. Assessments were made of the direct effects of sleep disturbance, as well as the indirect effects of sleep disturbance, on the measures of pain.

Worse sleep disturbance scores were associated with greater depression, anxiety and catastrophizing, lower global positive affect, and worse functioning. The effect of sleep disturbance on the measures of CLBP were both direct (independent of other measures), as well as indirect, mediated by elevated emotional distress, lower positive affect and greater catastrophizing.

Conclusion: This study of patients with chronic low back pain found that greater sleep disturbance is associated with greater pain intensity and pain related symptoms, both through sleep disturbance itself and through the effect of sleep disturbance on psychosocial factors.

Burgess, H., et al. Associations between Sleep Disturbance and Chronic Pain Intensity and Function: A Test of Direct and Indirect Pathways. **Clin J Pain.** 2019, March; 35(7): 569-576.

FORCES OF ACUTE VS CHRONIC BAREFOOT RUNNING

Previous studies have shown that changing from shod to barefoot running can induce several acute changes in running biomechanics. This study assessed the biomechanics of those who have habituated to barefoot running.

Healthy, physically active adults, between 18 and 35 years of age, were recruited. None had experience with barefoot running. The subjects were randomized to a barefoot intervention group, a shod intervention group or passive control group. The subjects participated in seven sessions, separated by one week. For running habituation, the subjects ran in the intervention footwear (barefoot or shod) for 15 minutes on the treadmill at 70% of their VO2 max. The shod group wore a commercially available cushioned running shoe. Before and after the intervention, a running gait analysis was conducted on an instrument treadmill. The primary outcome measure was the foot strike index, calculated as the distance from the heel to the center of pressure at ground contact, divided by the foot/ shoe length. Secondary outcome variables were the angle of the ankle, foot and knee at foot strike.

Of the sixty participants, those in the barefoot group experienced improvement in the foot strike index and ankle, foot, and knee angles at ground contact ($p<0.001$), as well as vertical average loading rate ($p=0.003$), peak force ($p<0.001$) and acute reduction in loading rates. After habituation, however, the force and average loading rates increased towards baseline.

Conclusion: This study found that, while moving from shod to barefoot running will initially decrease forces, after habituation to this running condition, the forces will again increase.

Hollander, K., et al. Adaptation of Running Biomechanics to Repeated Barefoot Running: A Randomized Controlled Study. **Am J Sport Med.** 2019, July; 47(8): 1975-1983.

CAFFEINE AND EXERCISE INDUCED HYPOGLYCEMIA

Caffeine is an ergogenic substance used by athletes during sports practice. Despite its widespread use, mechanisms of action of caffeine remain incompletely understood. This study reviewed the effects of caffeine on blood sugar levels among runners.

Subjects were competitive long-distance runners, ages 18 to 40 years, with a body mass index averaging 22.3 kg/m². The athletes were randomized to receive a placebo or a tablet containing caffeine (6mg/kg) ingested 30 minutes prior to each stress test. Before and after each maximum stress test, heart rate (HR), blood pressure (BP), and subjective perception of effort (SPE), and labs (glucose, lactate [LAC], and triglyceride [TG]) were assessed. At the following appointment, the subjects were then tested after ingesting the alternate capsule.

Glycemic levels were significantly higher in the caffeine group than in the placebo group beginning at 11 minutes and continuing through the end of the thirty-minute protocol ($p<0.05$). In addition, triglyceride levels were higher in the caffeine group than in the placebo group before and after the stress test ($p<0.05$). Lactate levels however were lower after exercise in the caffeine group than in the placebo group ($p<0.05$).

Conclusion: This study of trained runners found that a supplemental dose of caffeine can increase glucose and triglyceride availability and reduce blood lactate concentration in athletes participating in a maximal stress test.

Weber, V., et al. Caffeine Prevents Exercise Induced Hypoglycemia in Trained Runners. **J Human Sport Exerc.** 2019; 14 (2): 335-347.

RIMEGEPANT FOR MIGRAINE

Migraine affects nearly one million people worldwide. As calcitonin gene -related peptide plays a role in the pathophysiology of migraine, this study assessed the treatment efficacy of an orally administered, calcitonin gene-related peptide receptor antagonist, rimegepant, for the treatment of acute migraines.

Subjects were adults with a one-year history of migraine, with an onset before the age of 50 years. The participants were randomized to receive a placebo, or 75 mg of rimegepant, to be taken with the occurrence of a migraine of moderate or severe intensity. The patients completed an electronic diary for up

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to 48 hours after taking the trial agent. They recorded pain intensity, associated symptoms, and functional disability up to 48 hours after the dose. The primary efficacy endpoint was freedom from pain and freedom from the patient's most bothersome symptom (MBS) associated with migraine.

A total of 1,186 patients at 49 treatment centers were studied. At two hours after ingestion, 19.6% of the rimegepant group and 12% of the placebo group were free from pain ($p<0.001$). Also, at two hours, 37.6% of the rimegepant group and 25.2% in the placebo group recorded freedom from their MBS ($p<0.001$). Serious adverse events were reported by one patient in the treatment group (back pain) and two patients in the placebo group.

Conclusion: This study of patients with acute migraine headaches found that 75 mg of oral rimegepant is superior to placebo in reducing pain, and the patient's most bothersome symptom, within two hours of ingestion.

Lipton, R., et al. Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine. **N Engl J Med**. 2019, July 11; 381 (2): 142-149.

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