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ALCOHOL CONSUMPTION AND MORTALITY

Previous studies have demonstrated an association between alcohol consumption and overall mortality, often described as a “J” shaped curve. However, no consensus yet exists concerning the optimal dose at which major benefits accrue. This study performed a dose response analysis, evaluating survival levels according to levels of alcohol consumption.

This study included 88,077 participants in the population based Cohort of Swedish men (COSM) and the Swedish Mammography Cohort (SMC). Subjects were assessed for baseline age, body mass index, smoking status, educational level and lifestyle factors, including alcohol consumption. Mortality was compared by alcohol consumption categories.

Among women, after adjusting for potential confounders, any category of alcohol consumption was found to be associated with substantially improved survival. A rapid increase in survival was found for women up to six g per day, where the improvement in survival was about 1.5 years as compared to lifetime abstainers. Among men, those with an intake of 10 to 15 g per day lived 1.3 years longer than lifetime abstainers, with survival time improving up to 15 g per day. The increase in survival seemed related to a decreased risk of cardiovascular disease for men and of both cardiovascular disease and cancer for women.

Conclusion: This study found that alcohol consumption of up to two drinks per day on average was associated with longer survival in both men and women, with the greatest benefits achieved with 0.5 to one drink per day for women and one to two drinks per day for men.

Bellavia, A., et al. Alcohol Consumption and Mortality: A Dose Response Analysis in Terms of Time.

Ann Epidemiol. DOI:10.1016/j.annepidem.2013.12.013. 2014.

JOGGING AFTER TOTAL HIP ARTHROPLASTY

Total hip arthroplasty (THA) is often sought by patients who wish to return to a more active lifestyle. This study investigated the number of patients who participate in jogging after THA, the parameters surrounding this decision, and the short-term clinical and radiographic results of those who chose to jog.

Subjects were patients undergoing THA between January of 2005 and May of 2011. Those who did jog after surgery answered questions regarding jogging frequency, distance, velocity, and symptoms. Those who did not jog were asked to give reasons why they did not participate. The subjects were administered the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) self-assessment questionnaire and the University of California – Los Angeles (UCLA) activity scales. Radiographs were reviewed to identify implant loosening, wear or osteolysis.

Of the 608 patients undergoing surgery, 33 were habitual preoperative joggers and 23 continued after surgery. The mean frequency of postoperative jogging was four times per week, with a mean distance per session of 3.6 km. Joggers had significantly lower mean scores for pain ($p = 0.03$) and physical function ($p = 0.02$) compared with non-joggers. For the postoperative UCLA activity score, joggers had a significantly higher score ($p < 0.0001$). No joggers showed hardware loosening, abnormal migration or excessive wear at a mean of five years' follow-up. Of the patients who did not participate in post-operative jogging, 511 responded that they had no interest, while 74 reported they had

an interest but did not participate. Most of them cited anxiety as the reason.

Conclusion: This study of patients undergoing total hip arthroplasty found that only 3.8% participated in jogging following surgery. No excessive wear was found among joggers at five-year follow-up.

Abe, H., et al. Jogging after Total Hip Arthroplasty. *Amer J Sports Med.* 2014, January; 42(1): 131–137.

HIGH CHOLESTEROL AND LONG-TERM SURVIVAL AFTER ISCHEMIC STROKE

Treatment with statin medications is associated with a reduced recurrence of ischemic stroke, with improvement in survival and functional outcome up to one year after stroke. However, other studies have also indicated a positive association between elevated cholesterol at ischemic stroke onset and improved short-term functional outcomes and 10-year survival. This study sought to further clarify the effects of cholesterol levels and the impact of statin treatment on short and long-term survival after acute ischemic injury.

This retrospective study included patients admitted to the stroke unit of the Karolinska University Hospital. Clinical and biochemical data were obtained by record review. All participants underwent admission computed tomography and/or magnetic resonance tomography of the brain, echocardiogram, carotid ultrasound and lab work, and were followed for up to seven years.

Of the 169 one-month survivors, 159 had available data regarding admission cholesterol. Three-month survival rates were 92% and 100% in the low and high cholesterol groups, respectively. The one, two, and five-year survival rates were 87%, 81%

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and 57% in the low cholesterol group, and 98%, 95% and 84% in the high cholesterol group ($p=0.001$).

The annual mortality rate in patients with low cholesterol was approximately seven percent after the first year, reaching 58% by the end of the observation period in the low cholesterol group. In contrast, the high cholesterol group had an annual mortality of three percent, reaching 31% after seven years. A multivariate analysis revealed that low admission cholesterol was an independent predictor of long-term mortality after adjusting for age at admission and NIHSS scores.

Conclusion: This retrospective study found that, in patients with acute ischemic stroke, higher admission cholesterol levels were associated with improved long-term survival.

Markaki, I., et al. High Cholesterol Levels are Associated with Improved Long-Term Survival after Acute Ischemic Stroke. **J Stroke Cerebrovasc Dis.** 2014, January; 23 (1): E 47-E 53.

DIET PATTERNS IN MIDLIFE AND AGING

Maintaining health in an aging population is a major challenge. While literature has demonstrated the role of diet in mortality, there is a relative lack of data concerning the role of dietary patterns and their effect on overall healthy aging. This study examined the association between dietary patterns in midlife and healthy aging.

Data were obtained from the Nurses Health Study, begun in 1976 with a cohort of female nurses, ages 30 to 55 years. In 1980, the participants completed a semi-quantitative food frequency questionnaire, which was repeated in 1984, 1986 and every four years thereafter. Dietary quality was assessed using the Alternative Healthy Eating index-2010 (AHEI-2010), and the Alternate Mediterranean Diet Scores (a-MeDi). Healthy aging was assessed at 15 years' follow-up, defined as survival to 70 years without one of 11 major chronic diseases, no major impairments in cognition, no physical disabilities and intact mental health.

At follow-up, 11% were considered healthy agers and 89%

were considered usual agers. Compared with usual agers, healthy agers had a lower prevalence of obesity and tobacco abuse, and exercised more at midlife. Multivariable analysis revealed that greater adherence at midlife to AHEI-2010 and a-MeDi diets were both strongly associated with greater odds of healthy aging ($p<0.001$ and $p=0.002$ respectively).

Conclusion: This study demonstrates that adherence to better dietary patterns in midlife is associated with better health and function among those surviving to an older age.

Samieri, C., et al. Association between Dietary Patterns at Midlife and Health in Aging. **Ann Intern Med.** 2013, Nov; 159(9): 584-591.

MEDITERRANEAN DIET AND PERIPHERAL ARTERY DISEASE

Adherence to a Mediterranean diet is thought to reduce the risk of myocardial infarction and stroke. Thus, some have hypothesized that this diet could be effective in reducing the risk of peripheral artery disease (PAD). This study explored the association between adherence to a Mediterranean diet and symptomatic PAD.

This randomized, primary prevention trial included men ages 55 to 80 years of age and women 60 to 80 years of age, all without clinical PAD. All had diabetes mellitus or at least three cardiovascular risk factors. The patients were randomized to one of three groups, a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with nuts, or counseling concerning a low-fat diet. All participants received comprehensive dietary education on a quarterly basis. A confirmed diagnosis of PAD in symptomatic patients served as the primary endpoint.

Of the 8,713 eligible candidates, 7,477 were initially randomized. At five-year follow-up, both intervention groups had a lower risk of PAD, as compared to the control group. While the risk of PAD was slightly lower in the olive oil supplementation group than in the nut supplementation group, no significant difference was found between the two Mediterranean diet groups.

Conclusion: This randomized, primary prevention trial targeting individuals with diabetes and/or cardiovascular risk factors, found that a Mediterranean diet can reduce the risk of peripheral artery disease.

Ruiz-Canela, M., et al. Association of Mediterranean Diet with Peripheral Artery Disease: The PREDIMED Randomized Trial. *JAMA*. 2014, January 22/29; 311(4): 415-417.

OBESITY AND LATE AGE SURVIVAL AND MORBIDITY AMONG OLDER WOMEN

As obesity is thought to be a modifiable risk factor for physical disability, this study investigated whether obesity in older women is related to survival to 85 years of age without major disease or disability.

The sample was taken from the Women's Health Initiative observational study and clinical trial programs which studied postmenopausal women 50 to 79 years of age, recruited from 40 U.S. clinical centers. At enrollment, the participants completed questionnaires concerning demographic characteristics, health behaviors and medical history. All patients were measured for body mass index and waist circumference (WC). Major chronic diseases were recorded, with disabilities documented.

A total of 27,532 women lived to 85 years of age. At 85 years of age, 12.0% of healthy-weight women were classified as mobility disabled, while for women in the obese I, II, and III groups at baseline, the proportions were 25.5%, 33.3%, and 34.1%, respectively. Of women with a baseline WC greater than 88 cm 24.8% were mobility disabled compared with 14.2% of women with a baseline WC of 88 cm or less. In addition, the risk of earlier death was higher among obese women than among normal weight women.

Conclusion: This study of women with a baseline age range of 66 to 81 years found that obesity and higher waist circumference are associated with increased risk of mortality and of developing mobility disability by the age of 85 years.

Rillas-Sun, E., et al. Obesity and Late-Age Survival without Major Disease or Disability in Older

Women. *JAMA Intern Med*. 2014, January; 174(1): 98-106.

LOW BACK PAIN AND ABNORMAL FOOT FUNCTION

While abnormal foot posture has been proposed as a mechanism for low back pain (LBP), this relationship has not been well studied. This study analyzed data from the Framingham Foot Study cohort to further investigate this relationship.

The Framingham Foot Study cohort was derived from members of the Framingham Study's original cohort, and the Framingham offspring cohort. Participants underwent a physical examination of the foot between 2002 and 2005. Foot posture and function were both assessed using the Matscan system. In addition, LBP was documented with a structured questionnaire. Asymmetry of foot posture and foot function was assessed. Covariates in the analysis included age, sex, weight, smoking status and depressive symptoms.

Of the 3,370 participants, 1,930 had LBP and foot pressure data at the time of the analysis. The mean age of the participants was 64 years, with 55% female. Overall, neither foot posture nor function was associated with increased risk of LBP. However, among women, compared to the normal foot function reference group, those with pronated foot function had an increased likelihood of LBP ($p=0.011$).

Conclusion: This study found an association between foot posture and low back pain, but only among women.

Menz, H, et al. Foot Posture, Foot Function and Low Back Pain: The Framingham Foot Study. *Rheum*. 2013, December; 52(12): 2275-2282.

QUALITY-OF-LIFE AFTER SCOLIOSIS SURGERY

Scoliosis is often treated surgically when the Cobb's angle exceeds 45° to 50°. The success of this surgery is traditionally measured by radiographic changes, although these changes only weakly predict patient satisfaction. This study was designed to better understand the changes in quality-of-life experienced

by patients treated for scoliosis with surgery.

This study included data collected from the Swe-Spine registry, beginning in 1993 with registration of surgery in the lumbar spine. All patients were diagnosed with idiopathic, congenital or neuromuscular scoliosis. Before surgery the Cobb angles of the primary curves were obtained. In addition, the EuroQol (EQ-5D) and the Scoliosis Research Society 22r instrument (SRS-22r) were answered by the patients after surgery and at one and two years postoperatively.

A total of 211 patients were included. The EQ-5D scores improved at two-year follow-up in the idiopathic group ($p=0.001$), in the congenital group ($p=0.07$) and in the neuromuscular group ($p=0.06$). By examining specific domains, at two years, pain and anxiety scores were improved in all groups. Improvements were also found for all groups in scores on the SRS-22r for pain function and quality of life, with the least improvement noted in the congenital group.

Conclusion: This study of patients undergoing surgery for scoliosis found that pain and quality-of-life significantly improved in those with idiopathic or neuromuscular scoliosis, with the least effect seen in those with congenital scoliosis.

Ersberg, G., et al. Pre-and Postoperative Quality-of-Life in Patients Treated for Scoliosis. *Acta Orthopædica*. 2013, December; 84 (6): 537-543.

PROLONGED RELEASE OXYCODONE-NALOXONE FOR RESTLESS LEG SYNDROME

Dopaminergic drugs are recommended as a first-line treatment for restless leg syndrome (RLS). However, some studies have shown that prolonged use of these medications can result in lost efficacy and problems with tolerability. As an off-label use, opioids are thought to be an effective second line treatment. This study investigated the efficacy of prolonged release oxycodone-naloxone in the treatment of severe RLS.

This 12-week, double-blind, placebo-controlled trial included patients diagnosed with RLS, with at least six months of symptoms. Those

in the treatment group received a starting dose of oxycodone 5 mg and naloxone 2.5 mg, twice per day, which could be titrated up to oxycodone 40 mg and naloxone 20 mg. Once stabilized, treatment was maintained for a further six weeks. The primary endpoint was the International Restless Leg Syndrome Study Group Severity Rating Scale, measured as change from baseline to 12 weeks.

A total of 306 patients were included in the randomization, with 154 assigned to a placebo group and 150 assigned to the treatment group. The change in international RLS Study Group Severity Rating Scale sum scores at 12 weeks was significantly greater for the treatment than the placebo group ($p < 0.0001$). During the treatment phase, treatment related adverse events were reported by 73% of the treatment group and by 43% of the placebo group.

Conclusion: This study of patients with restless leg syndrome suggests that prolonged release oxycodone-naloxone may be effective in reducing symptoms.

Trenkwalder, C., et al. Prolonged Release Oxycodone-Naloxone for Treatment of Severe Restless Leg Syndrome after Failure of Previous Treatment: A Double-Blind, Randomized, Placebo-Controlled Trial with an Open Label Extension. *Lancet-Neurol.* 2013, December; 12: 1141-1150.

REFORMULATION IN EXTENDED-RELEASE OXYCODONE AND ABUSE

Misuse of prescription opioid analgesics is of growing concern. Those who abuse long-acting opioid medications often alter the tablets by crushing, dissolving or chewing the medication to bypass the controlled release delivery system. To counter this problem, the makers of OxyContin reformulated the medication to counter tampering. This study assessed the effect of this reformulation.

Data were obtained from the poison center and drug diversion programs of the Research Abuse Diversion and Addiction Related Surveillance System (RADARS). Data were reviewed for the two years before and the two years after the

release of reformulated extended-release OxyContin. Data were reviewed for the number of abuse exposures, therapeutic error exposures and diversion into illegal markets.

The average extended release opioid (ERO) abuse exposure in the post-reformulated period was 38% less than that of the period prior to the introduction of this medication ($p < 0.001$). The average abuse exposure population rates for the other prescription opioids did not significantly differ during the same time periods. Therapeutic error exposures declined 24% in the general population. The average ERO diversion rate was 53% less than the average rate before the introduction of reformulated ERO.

Conclusion: This study suggests that tamper-resistant extended-release oxycodone may be effective in reducing the misuse of this medication.

Severtson, S., et al. Reduced Abuse, Therapeutic Errors, and Diversion following Reformulation of Extended-Release Oxycodone in 2010. *J Pain.* 2013, October; 14(10): 1122-1130.

BRAIN NEUROTROPHIC FACTOR AND DEMENTIA

Previous studies have demonstrated that brain derived neurotrophic factor (BDNF) is highly expressed throughout the central nervous system. Reduced levels have been observed in the hippocampus and parietal lobe, as well as the serum, of people with mild cognitive impairment and Alzheimer's disease (AD). This study was designed to determine whether serum BDNF levels are associated with the risk for incident dementia and AD.

Data were obtained from the Framingham Heart Study, initiated in 1948, and the offspring study initiated in 1971. Serum BDNF concentrations were measured on previously frozen blood samples. As all Framingham Heart Study participants are under continuous surveillance for impaired cognitive function, these data were available to determine the associations between BDNF and incident dementia and AD.

During a median of 10 years' follow-up, 140 participants developed dementia, with 117 developing AD. After controlling for age, gender and

cohort, each standard deviation increment of serum BDNF levels was associated with a 23% lower risk for future dementia ($p = 0.006$) and PD ($p = 0.01$). Compared with the lowest quintile, the top quintile of BDNF levels was associated with less than half the risk for developing AD and other dementias. However, the association between BDNF level and risk for dementia and PD was significant only in women, people age 80 years or older, and participants with a college degree.

Conclusion: This community based cohort study of dementia free individuals found that higher levels of BDNF are associated with a reduced risk of developing Alzheimer's disease and other forms of dementia, with this association only apparent in women, those older than 80 years of age and those with a college degree.

Weinstein, G., et al. Serum Brain Derived Neurotrophic Factor and the Risk for Dementia: The Framingham Heart Study. 2014, January. *JAMA Neurol.* 2014, January; 71(1): 55-61.

COGNITIVE ACTIVITY AND DURATION OF POSTCONCUSSIVE SYMPTOMS

While cognitive rest is often recommended after a concussion, limited data are available to support this recommendation. This study assessed the independent effect of cognitive activity on symptom duration.

This single center, prospective cohort study included patients presenting to the Sports Concussion Clinic of Boston's Children's Hospital between 2009 and 2011. The participants were assessed for cognitive activity, using the Cognitive Activity Scale, and for concussion, using the Post-Concussion Scale Score (PCSS). Patients were considered recovered when they were symptom free and no longer taking medications prescribed for concussion symptoms. The primary outcome variable was the duration of concussion symptoms.

During the study period, 335 participants qualified for inclusion in the analysis. The mean duration of symptoms was 43 days. Univariate modeling indicated that patients in the highest quartile of cognitive activity days took significantly longer to recover than did those in the first to

third quartiles. Multivariate Cox proportional hazards modeling revealed that the total score on the PCSS at the initial visit and cognitive activity days were independently associated with the duration of symptoms. Interestingly, gender, age, loss of consciousness, amnesia, and number of previous concussions were not independently associated with time to symptom resolution.

Conclusion: This study of children with concussions found that extensive cognitive activity after concussion is associated with a longer time to recover.

Brown, N., et al. Effect of Cognitive Activity Level on Duration of Post-Concussion Symptoms. *Pediatrics*. 2014, February 1; 133(2): e299-e304.

MENSTRUAL PHASE AND OUTCOME AFTER MILD TRAUMATIC BRAIN INJURY

Some data suggest that women have a higher incidence of mild traumatic brain injury (MTBI) than men who play similar sports. Other studies have found better post-TBI outcomes for women than men among premenarche or postmenopausal women. This study compared the outcomes of women by the phase of menstrual cycle at the time of injury.

Female patients between the ages of 16 and 60 years who presented to the emergency department within four hours of MTBI were considered for this study. Admission serum progesterone level was used to determine the menstrual cycle phase at the time of injury. For comparison, the patients were divided into a synthetic progestin (SP) group, a follicular phase (FP) group, and a luteal phase (LP) group. In addition, CT results were obtained, and one-month outcome was assessed by phone using the Rivermeade Postconcussion Questionnaire (RPCQ) and quality of life with the EuroQol/EQ5D. The primary outcome measure of interest was post-concussive symptoms at one month using the RPCQ. Outcomes were compared by menstrual phase.

The EuroQol/EQ5D index differed significantly between groups, with the SP group obtaining the highest scores and the LP group the lowest scores. The LP group was the most symptomatic, as measured by RPCQ

scores, although, across all measures, none of the differences were statistically significant. For all outcomes, subjects in the LP group had approximately twice the odds of scoring worse on the outcome scale than did subjects in the FP group. The authors suggest that these findings support the hypothesis that the acute withdrawal of progesterone after mild traumatic brain injury may worsen the outcome.

Conclusion: This study of women 16 to 60 years of age with a mild traumatic brain injury found that those in the luteal phase of the menstrual cycle at the time of injury have worse outcomes than do women in the follicular phase, or who were taking synthetic progestins.

Wunderle, K., et al. Menstrual Phase as a Predictor of Outcome after Mild Traumatic Brain Injury in Women. *J Head Trauma Rehab*. 2014. DOI: 1097/HTR.0000000000000006

RECANALIZATION WITH HYPOTHERMIA AFTER ISCHEMIC STROKE

Therapeutic hypothermia (TH) has been found to have neuroprotective effects in experimental stroke models. Animal studies have suggested that TH may be more effective for those with severe stroke after successful recanalization. This study investigated the effects of mild hypothermia among patients with large hemispheric acute ischemic strokes with successful recanalization.

This multicentered study included consecutive patients admitted with an acute ischemic stroke involving the anterior circulation. Eligible patients had an acute cerebral infarction with endovascular recanalization within six hours of symptom onset. In center A, the patients were cooled to 35°C, while in center B, the patients were treated with the same protocol, without hypothermia. The subjects were followed by CT examination for hemorrhagic transformation cerebral edema and for medical complications. The clinical outcomes were assessed by serial National Institutes of Health Stroke Scale (NIHSS) scores as well as by modified Rankin Scale scores.

Of the 75 patients identified, 39 were randomized to the hypothermia group and 36 to the non-hypothermia group. Hypothermia was associated

with less hemorrhagic transformation [39% versus 14% ($p=0.016$)] and less cerebral edema ($p=0.001$). The hypothermia group had a higher proportion of good outcomes at three months, with no difference between groups in mortality. Medical complications did not differ between the two groups, except for pneumonia, which was significantly higher in the normothermia group ($p=0.004$).

Conclusion: This randomized study found that, in patients with ischemic stroke, after successful recanalization, therapeutic hypothermia may reduce the risk of cerebral edema and hemorrhagic transformation, leading to improved clinical outcomes.

Hong, J., et al. Therapeutic Hypothermia after Recanalization in Patients with Acute Ischemic Stroke. *Stroke*. 2014, January; 45: 134-140.

C-REACTIVE PROTEIN AND HEMORRHAGIC STROKE

After spontaneous intracerebral hemorrhage (sICH), early hematoma growth (EHG) occurs in 20 to 40 percent of patients, resulting in a worse prognosis. As inflammation is a major feature of intracerebral hemorrhage pathology, C-reactive protein (CRP) has been associated with 30-day mortality among these patients. However, its relationship to early hematoma growth (EHG) is unknown. This study was designed to determine the relationship between CRP and EHG after sICH.

This prospective, multi-center observational study included patients 18 years of age or older, with a diagnosis of sICH. Patients were included in the analysis if they presented within six hours of onset, had CRP determined at study entry and completed clinical and imaging data. An initial CT was obtained at admission, with a second CT at 24 hours (or earlier if clinically indicated). The primary outcome variable was EHG, as defined by absolute growth of greater than 12.5 cm³, or relative growth of greater than 33% as measured by a follow-up CT.

Among the 215 men and 184 women included in the final analysis, EHG occurred in 25.8%, occurring more often among those with early neurologic worsening ($p<0.001$). A univariate analysis revealed that EHG

and early neurologic worsening were significant more frequent, and hemorrhagic growth significantly greater, among those with a CRP of above 10 mg/ml.

Conclusion: This study of patients with spontaneous intracerebral hemorrhage found that elevated plasma C-reactive protein within the first few hours of hemorrhage is associated with both early hemorrhagic growth and early neurologic worsening.

Napoli, M., et al. C-Reactive Protein Predicts Hematoma Growth in Intracerebral Hemorrhage. **Stroke**. 2014, January; 45(1): 59-65.

MEMANTINE AND GAIT SAFETY IN ALZHEIMER'S DISEASE

A limited number of studies have suggested that, among patients with dementia, both memantine and donepezil use may reduce gait variability. This study compared these medications with regard to their ability to affect gait in patients with Alzheimer's disease (AD).

This prospective, nonrandomized, case-control trial included patients with mild to moderate AD and related disorders (ADRD), treated with an acetylcholinesterase inhibitor (donepezil), a NMDA receptor antagonist (memantine), or no medication. All subjects underwent gait analysis, with measurements including the coefficient of variation of stride time and walking speed.

Stride time decreased significantly after medication, with this change due to memantine ($p=0.01$) more than to donepezil ($p=0.084$).

Conclusion: This pilot study of patients with Alzheimer's disease suggests that treatment with memantine may result in improvement in gait, with no such findings seen for those treated with acetylcholinesterase inhibitors.

Beauchet, O., et al. Anti-Dementia Drugs and Changes in Gait: A Pre-Post, Quasi Experimental, Pilot Study. **BMC Neurol**. 2013, 13: 184.

NOVEL ORAL ANTICOAGULANTS AND INTRACRANIAL HEMORRHAGE

Individual trials have shown a decreased risk of intracranial

hemorrhage (ICH) with use of novel oral anticoagulants (NOACs). Currently, three such medications are approved for stroke prevention in patients with atrial fibrillation. These include dabigatran, rivaroxaban and apixaban. This study was designed to better understand the relative risk of each of these medications for ICH.

This meta-analysis reviewed databases for randomized trials which contained studies of the relevant NOACs. Six, randomized trials compared one of these NOACs with conventional warfarin or aspirin. Endpoints abstracted from the studies included ICH and/or hemorrhagic stroke.

The authors identified six studies with NOACs compared with warfarin and aspirin, enrolling a total of 57,491 patients. The mean time in the therapeutic range was 61.2% for warfarin, with a minimum duration of follow-up of 12 weeks, and a maximum of two years. The absolute risk of ICH was 0.52% for dabigatran, 0.78% for rivaroxaban and 0.52% for apixaban, as compared to 1.24% for warfarin. The differences between the NOACs did not reach statistical significance.

Conclusion: This review and meta-analysis found a reduced risk of intracranial hemorrhage with the use of novel oral anticoagulant medications, as compared with warfarin or aspirin.

Chatterjee, S., et al. New Oral Anticoagulants and the Risk of Intracranial Hemorrhage. Traditional and Bayesian Meta-Analysis and Mixed Treatment Comparisons of Randomized Trials of New Oral Anticoagulants in Atrial Fibrillation. **JAMA-Neurol**. 2013, December; 70 (12): 1486-1490.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG USE WITH STABLE ATHEROTHROMBOTIC DISEASE

Previous studies have outlined the risk of prescribing nonsteroidal anti-inflammatory drugs (NSAIDs) to patients with a history of myocardial infarction. The American Heart Association update for clinicians has issued a consensus statement concerning the cautious use of these agents in patients with a history of cardiovascular disease. This study

further evaluated this risk in patients with stable atherothrombotic disease.

Subjects were obtained from the Reduction of Atherothrombosis for Continued Health (REACH) registry, a large, multi-national registry of outpatients with stable atherothrombotic disease. The patients were 45 years of age, all with established atherothrombotic disease or at least three risk factors for atherothrombotic disease.

The use of aspirin and other antiplatelet agents, including NSAIDs, was assessed at the baseline visit, as well as at annual follow-up visits. Cardiovascular outcomes were recorded, including the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and ischemic hospitalization. The use of medications was compared with subsequent myocardial events.

Of the 44,095 patients in the database, 4,420 used NSAIDs at baseline. Univariate analysis revealed significantly higher rates of cardiovascular death/myocardial infarction/stroke/hospitalization, hospitalization for heart failure and hospitalization for ischemic events among those who used NSAIDs ($p<0.001$ for all). After adjustment, NSAID use was associated with a 1.16 higher risk of cardiac vascular death, myocardial infarction or stroke, and a 1.12 higher risk of cardiovascular death, myocardial infarction, stroke, ischemic hospitalizations. Patients taking NSAIDs also had a higher risk of nonfatal myocardial infarction, nonfatal stroke, heart failure hospitalization and ischemic hospitalization, as compared to nonusers.

Conclusion: This observational study found that, among patients with stable atherosclerotic disease, the use of NSAIDs is associated with a significantly increased risk of major adverse cardiovascular outcomes.

Kohli, P., et al. NSAID Use and Association with Cardiovascular Outcomes in Patients with Stable Atherothrombotic Disease. **Am J Med**. 2014, January; 127(1): 53-60.

TRANSCRANIAL DIRECT CURRENT STIMULATION IN LUKOARAIOSIS

Lukoaraiosis involves hyperintensities in the cerebral

subcortical white matter, with associated gait and balance dysfunction. There are no proven treatments for gait disorder and balance dysfunction in these patients. This study evaluated the use of transcranial direct current stimulation (tDCS) to augment the effects of physical therapy training in the treatment of patients with lukoaraiosis.

This double-blind study included nine patients with lukoaraiosis, all with gait and balance disturbances, and 18 healthy controls. The subjects were randomized to receive either tDCS or sham stimulation during physical therapy training. This process was repeated one week later, with the stimulation situation reversed, in a double-blind design. The stimulation included a 2 mA current delivered during exercise for 15 minutes. The patients were assessed for gait velocity, stride length, stride length variability, six meter walk test results and quantitative retropulsion test results.

Patients in the control group performed significantly worse on all tests than did the treatment group. Significant improvements were noted in the treatment group in gait velocity ($p=0.008$), stride length ($p=0.05$), stride length variability ($p=0.02$), timed up and go duration ($p=0.042$), the six meter walk test ($p=0.03$) and the retropulsion test ($p=0.045$). *Post-hoc* analysis revealed no effect of physical therapy alone.

Conclusion: This randomized, controlled study of patients with lukoaraiosis found that the combination of transcranial direct current stimulation and locomotor training can improve clinically relevant locomotor performance.

Kaski, D., et al. Improving Gait and Balance in Patients with Lukoaraiosis Using Transcranial Direct Current Stimulation and Physical Therapy Training: Exploratory Study. *Neurorehab Neural Repair*. 2013, November/December; 27: 864-871.

BIOLOGIC THERAPY AND FUNCTION IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disease causing inflammation and pain, with a potential serious loss of function. In recent years, new biologically

engineered medications have been introduced, which either block tumor necrosis factor-A (TNF) or otherwise influence the system. This meta-analysis investigated the magnitude of the benefits of these biologic agents on the functional capacity of patients diagnosed with RA.

A systematic literature search was performed to identify studies involving adult patients with a diagnosis of RA, treated with biologic agents including abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab or rituximab. The primary outcome measure was the standardized mean difference (SMD) in change from baseline on the Health Assessment Questionnaires (HAQ), comparing biologic and non-biologic disease-modifying anti-rheumatic drugs (nbDMARDs).

Of the studies reviewed, 35, randomized, controlled trials were included, involving 8,733 individuals in the treatment groups and 4,664 in the control groups. Taking all RCTs together, a mean superiority of biologic treatment compared with MTX/nbDMARD treatment was found. On the SMD of the HAQ scale, biologics led to a 0.32 greater improvement in functional capacity in early RA patients who were DMARD naive and to a 0.48 greater improvement in DMARD inadequate responders.

Conclusion: This meta-analysis of studies involving patients with rheumatoid arthritis found that biologics are superior to nbDMARDs, with likely minor differences between them.

Callhoff, 2013; 52(12) Impact Of Biologic Therapy on Functional Status in Patients with Rheumatoid Arthritis—A Meta-Analysis. *J Rheum*. 2013, December; 52(12): 2127-2135

INJECTION SAFETY IN PATIENTS ON WARFARIN

While some studies suggest that joint or soft tissue injections are relatively safe for patients undergoing anti-coagulation, many recommend reversing anti-coagulation before administering these procedures. This study was designed to further understand the safety of these joint injections in patients prescribed warfarin.

This study reviewed the outcomes of patients before and after a protocol

change in a rheumatology department. The protocol prior to September of 2011 was to withhold warfarin for five days prior to an elective joint or soft tissue injection. At that time, warfarin was replaced with low molecular weight heparin, which was not given on the day of the procedure. After September of 2011, the new protocol allowed warfarin to be continued, with the procedure performed if the INR was less than three. All procedural complications within four weeks were identified through contact with the telephone helpline or with a medical practitioner.

In the initial cohort, 32 procedures were performed in 18 patients. No clinical hemarthroses or other complications occurred. In the later cohort, 32 procedures were performed in 21 patients. Among these patients, there were also no clinical hemarthroses or other complications. One patient, with a history of deep venous thrombosis, experienced a recurrence when warfarin was withheld for a joint injection.

Conclusion: This study of patients undergoing joint or soft tissue injections found no significant bleeding events among patients who received injections while taking warfarin and with the international normalized ratio within therapeutic range.

Hoo, J., et al. Safety of Joint and Soft Tissue Injections in Patients on Warfarin Anticoagulant Action. *Clinical Rheum*. 2013, December; 32(12): 1811-1814.

PHYSICAL ACTIVITY AND ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a common, inflammatory rheumatic disease which causes characteristic inflammatory back pain. Treatment guidelines recommend exercise as important for disease management. This study compared physical activity levels and exercise habits of patients with AS with high disease activity versus those with low disease activity.

This cross-sectional study included patients diagnosed with AS who were 70 years of age or younger. The AS disease activity score (ASDAS) was used to assess disease activity, and the Bath Ankylosing Spondylitis Functional Index (BASFI)

(Continued from page 2)

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was used to assess physical function. Physical activity was measured with the International Physical Activity Questionnaire-Long.

Data were included for 149 patients with AS and 133 controls. Patients with high disease activity had significantly lower energy expenditure than those with low disease activity ($p=0.02$) or controls ($p=0.01$). No differences were found between patients with low disease activity and controls. Patients with high disease activity were less likely to achieve predefined health enhancing physical activity levels than were the low disease activity patients ($p=0.02$). A larger proportion of patients with high disease activity reported participating in swimming ($p=0.04$) and fewer reported participating in hiking ($p=0.02$) as compared to patients with low disease activity.

Conclusion: This study of patients with ankylosing spondylitis found that those with high disease activity are less physically active and perform less vigorous activities than those with low disease activity.

Fongen, C., et al. High Disease Activity is Related to Low Levels of Physical Activity in Patients with Ankylosing Spondylitis. *Clin Rheum.* 2013, December; 32(12): 1719-1725.

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