MELD Predicts LVAD Complications, Mortality

Model for End-Stage Liver Disease Score Predicts Left Ventricular Assist Device Operative Transfusion Requirements, Morbidity, and Mortality.

In patients with severe heart failure who undergo left ventricular assist device implantation, the MELD score is significantly associated with perioperative transfusion requirements, severe morbidity, and death.

Background: Left ventricular assist devices (LVADs) are sometimes implanted as a bridge to heart transplantation. Bleeding during the procedure is the most common complication, occurring in 30% to 50% of patients. While some of the bleeding risk is associated with the surgical procedure, patient factors related to chronic severe congestive heart failure (CHF) have also been implicated. Important bleeding diatheses related to CHF include congestive hepatopathy and uremia or hepatic ischemia related to poor perfusion.

Objective: The current study was undertaken to examine whether an existing risk assessment tool, the Model for End-Stage Liver Disease (MELD) score, might be useful to predict bleeding risk in the implantation of LVADs. The MELD score is used to risk-stratify patients with cirrhosis before certain procedures (transjugular portosystemic shunts or major surgery) and has been used to assign priority for orthotopic liver transplantation. The MELD score is computed based on a patient's serum creatinine, total bilirubin, and international normalized ratio.

Design: This was a retrospective-single institution study.

Methods: Patient data and outcomes from 211 LVAD implantations were reviewed (1996 to 2007). The primary outcome was total perioperative blood product exposure (TBPE): the sum of packed red blood cells (PRBC), platelets, fresh frozen plasma (FFP), and cryoprecipitate administered in the perioperative period. Secondary outcomes were perioperative death, 6-month survival, and selected severe perioperative morbidities. MELD scores were calculated based on laboratory data <24 hours before operation.

Results: The median TBPE was 74 units (13 units of PRBCs, 30 units of platelets, 14 units of FFP, and 14 units of cryoprecipitate). In the cohort, perioperative deaths occurred in 14% of patients; the risk of death increased 30% per 10-unit increase in TBPE. The MELD score significantly correlated with TBPE (Pearson correlation coefficient, 0.33; P <0.001). In multivariate analysis, 5-point increases in MELD scores were associated with a 60% increased adjusted risk of perioperative death (OR, 1.6; 95% CI, 1.1 to 2.3; P <0.001). MELD scores were similarly correlated with important perioperative morbidity, such as prolonged ICU stays or requirement for hemodialysis. Higher MELD scores predicted decreased survival at 6 months.

Conclusions: MELD score predicted perioperative transfusion requirements, major morbidity, and death. MELD scores also predicted 6-month survival.

Reviewer’s Comments: This was a very clever study. The authors had the insight that much of the major morbidity and mortality of LVAD implantation was related to the bleeding diatheses that may be present in patients with severe heart failure. In addition, severe heart failure may increase bleeding risk by congestive or ischemic insults to the liver and kidneys. I suspect that the MELD score will be a part of patient selection for LVAD implantation as a bridge to transplantation, with the important caveats that this was a single-institution, retrospective study that should be replicated. (Reviewer-Paul R. Sutton, PhD, MD).

© 2010, Oakstone Medical Publishing

Keywords: Left Ventricular Assist Device, Bleeding Complications, Mortality, MELD Score

Print Tag: Refer to original journal article
Stress-Only vs Standard Stress-Rest Myocardial Perfusion Imaging


Chang SM, Nabi F, et al:

J Am Coll Cardiol 2010; 55 (January 19): 221-230

Stress-only SPECT imaging may be adequate for risk stratification in patients with a normal stress SPECT study.

**Background:** SPECT imaging is a standard evaluation for the presence and severity of coronary artery disease (CAD). Typical imaging compares stress perfusion to rest perfusion. However, in an era of increasing concerns about cost containment and reducing radiation exposure in a population with increasing-risk CAD, this may not be the optimal strategy. The concern with stress-only imaging is that patients with left main or significant 3-vessel disease may have normal stress imaging, and that the extent of disease may be identified only when stress is compared to rest images.

**Objective:** To evaluate the use of stress only versus stress/rest myocardial perfusion imaging in assessing mortality in patients evaluated for CAD.

**Methods:** 27,540 patients underwent SPECT imaging; 16,854 patients had normal scans and made up the study population. Of the imaging studies performed, 8034 were performed as stress only, and 8820 as stress/rest. The mean follow-up was 4.7 years. The primary end point was total mortality, using the Social Security Death Index to assess vital status. The Cox proportional hazards model could not be reliably used in this model; therefore, a time ratio (TR) was derived, with TR>1 defining an increased survival time, and TR<1 being a decreased survival time.

**Results:** Approximately 13% of patients died during the study, with an annual mortality of 2.5% to 3%. Deaths in those with normal SPECT imaging were more common in patients with diabetes mellitus (DM), older patients, nonobese patients, and inpatients. Multivariate predictors of death were increasing age, BMI <20 kg/m2, history of CAD, DM, history of smoking, inpatient status, and need for pharmacologic stress. When adjusted for baseline characteristics, there was no statistically significant difference in mortality in those who underwent stress-only imaging versus those with stress/rest imaging.

**Conclusions:** Patients with normal stress imaging have similarly low mortality rates as those who undergo stress/rest imaging. Therefore, patients with normal stress imaging do not require further rest imaging, which would decrease cost and radiation exposure.

**Reviewer's Comments:** This study suggests that the rest portion of a stress SPECT study could be deferred in patients with normal stress imaging performed with standard protocols and experienced interpretation. Both this study and others emphasize the need for truly "normal" scans if the rest imaging is to be avoided; if uncertain, the rest imaging must be performed. Using this paradigm will diminish cost and reduce patient radiation exposure. It is also likely to be adopted by payors in this era of cost containment. (Reviewer-Karen Stout, MD).

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Keywords: Coronary Disease, SPECT Imaging, Risk Stratification

Print Tag: Refer to original journal article
CACS adds to risk prediction of SPECT imaging in patients evaluated for CAD.

**Background:** Coronary artery calcium score (CACS) and stress perfusion (SPECT) imaging are standard evaluations for coronary artery disease (CAD) severity. However, a small proportion of patients with normal SPECT imaging go on to have myocardial infarction (MI) or cardiovascular death, whereas other patients with moderate or severe CAD by CACS do not have such events.

**Objective:** To determine if an integration of CACS and SPECT data provide improved risk prediction in asymptomatic patients without clinically evident CAD.

**Methods:** 1175 patients without a history of CAD who underwent both CACS and SPECT imaging for clinical reasons. Median time between studies was 57 days. Ischemia on ECG and SPECT imaging was determined by usual protocols, and CACS scores were determined by standard Agatston protocols. Clinical factors included a modified Framingham score, age, gender, smoking status, chest pain, history of hypertension, abnormal ECG, and whether exercise was the stress modality. Mean follow-up was 6.9 years. Total cardiac events, all-cause death, and MI were the primary end points.

**Results:** There was a relationship of abnormal SPECT with increasing CACS scores, with 1% abnormal CACS in patients with CACS <10 and 29% for patients with CACS >400. Those with normal SPECT imaging had low total (<1%) and all-cause death/MI event rates (<0.5%) over 4 years. There was a hazard ratio (HR) of 3.55 for any cardiac event and 2.75 for death/MI in patients with normal SPECT but CACS >400. The separation in survival curves occurred at 3 years for all cardiac events and at 5 years for death/MI.

**Conclusions:** CACS allows improved long-term risk prediction in those with normal SPECT imaging. The authors propose performing CACS in patients at intermediate/high CAD risk by clinical factors who have normal SPECT imaging to allow improved risk stratification.

**Reviewer's Comments:** In the ongoing quest to better risk-stratify patients with CAD, this study suggests a possible role of CACS that may be cost-effective. Given the current efforts to minimize costs and radiation exposure, this study would not obviously do either; therefore, further data are needed to suggest that there is actually an outcomes benefit to treatment decisions made differently based on the aggregate data obtained in SPECT/CACS testing. (Reviewer-Karen Stout, MD).

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Keywords: Coronary Disease, Risk Stratification, Coronary CT SPECT Imaging

Print Tag: Refer to original journal article
Will Statins Cure Aortic Stenosis?

Effect of Lipid Lowering With Rosuvastatin on Progression of Aortic Stenosis: Results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) Trial.

 Chan KL, Teo K, et al:

Circulation 2010; 121 (January 19): 306-314

Statins do not delay the progression of mild to moderate aortic stenosis.

Background: Aortic stenosis (AS) is a relatively common cardiac abnormality with typical progression from mild to moderate to severe over time. When AS is severe and symptomatic, the only currently effective treatment is aortic valve replacement (AVR). The progressive calcification of AS may be accelerated by hyperlipidemia, and retrospective studies suggest that statin use may slow the progression of AS. Because slowing the progression of AS may obviate the need for AVR, there is interest in medical therapy to slow the progression of disease.

Objective: To evaluate (1) whether statin use affects progression of mild to moderate AS, and (2) whether intensive statin treatment affects adverse outcomes associated with AS, such as cardiac death or AVR.

Design: Prospective, double-blind, placebo-controlled randomized trial.

Methods: Patients received either rosuvastatin 40 mg/day or placebo. Patients aged 18 to 82 years with mild to moderate AS (defined as aortic velocity 2.5 to 4.0 m/s) were recruited from echocardiography laboratories in participating Canadian centers. Patients with clinical indications for statin therapy were excluded. Target lipid levels were based on guideline assessment of individual risk. AstraZeneca provided rosuvastatin for the study and generated the randomization but did not otherwise have access to the data. Patients were followed up every 3 months for adverse effects, and annual echocardiograms were performed. Death and AVR were assessed in the usual fashion.

Results: Of 380 patients assessed, 272 were randomized. Almost half of both the rosuvastatin and the placebo groups discontinued treatment; therefore, 134 rosuvastatin and 135 placebo patients were included in intent-to-treat analysis, with 77 rosuvastatin and 69 placebo patients analyzed per protocol. As expected, LDL cholesterol did not change in the placebo group and decreased by 54% in the rosuvastatin group. There was no difference in AS progression or in AVR or cardiovascular death between groups. No cases of rhabdomyolysis developed, nor was there a significant difference in new cancer diagnosis between groups.

Conclusions: Rosuvastatin 40 mg did not change the progression of mild to moderate aortic stenosis in a group of patients not otherwise requiring a statin. Therefore, statins should not be considered as therapy for AS in patients with no other indication for lipid lowering.

Reviewer's Comments: Studies on valvular disease suffer from relatively small numbers and a very slowly progressive disease that often takes decades to manifest clinical significance. Thus, a 3- to 5-year window may not be adequate. The disease may have already progressed to the point where statins would not be useful if it is already moderate at the time of initiation. While the idea is appealing on many fronts, statins should not be used solely to slow progression of AS. (Reviewer-Karen Stout, MD).

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Keywords: Aortic Stenosis, Lipid Lowering, Statin

Print Tag: Refer to original journal article
Risk Assessment Beyond Just LDL?

Beyond Low-Density Lipoprotein Cholesterol: Respective Contributions of Non–High-Density Lipoprotein Cholesterol Levels, Triglycerides, and the Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio to Coronary Heart Disease Risk in Apparently Healthy Men and Women.

Arsenault BJ, Rana JS, et al:

J Am Coll Cardiol 2009; 55 (December 29): 35-41

Non–HDL-C, triglyceride, and non–HDL predict CAD risk regardless of LDL levels.

Objective: This is a substudy of the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Norfolk study, a population-based assessment of determinants of cancer.

Participants/Methods: Lipid levels were obtained in >25,000 participants aged 45 to 79 years at enrollment in 1993 to 1997. Diabetics were excluded, leaving 21,448 patients followed up for an average of 11 years. Lipid levels were classified by NCEP-ATP III criteria. Coronary artery disease (CAD) was defined in the usual fashion through data obtained from several databases; however, only inpatient admissions or deaths were available for assessment. Cox regression analysis was used. The hazard ratios (HR) were analyzed both by absolute values of lipids and by standard deviation (SD) increases.

Results: Of >9300 men, 1310 developed CAD; of 12,100 women, >770 developed CAD. Patients with CAD were older, had higher blood pressure, and had more abnormal lipid profiles. Usual co-morbidities were accounted for (including age, gender, smoking, and waist circumference). Hormone replacement therapy was also accounted for in women. Elevated non–HDL-C was a better predictor of risk than other lipids, with an HR of 2.39. When assessing based on SD increases, the HR for each SD increase in non–HDL-C was 1.54 versus 1.22 for LDL-C. Patients were also grouped by LDL levels to determine if there was increased risk related to non–HDL-C, triglyceride (TG), and non–HDL-C/TG ratio, regardless of LDL-C levels. Those with elevated non–HDL-C, TG, or non–HDL-C/TG ratio >5 had a higher risk of CAD, even if LDL-C levels were <100.

Conclusions: Non–HDL-C, TG, and non–HDL-C/TG ratio are predictors of CAD risk, regardless of LDL-C levels. The authors advocate changing guideline algorithms to include these measurements and suggest that lipid-lowering trials utilize non–HDL-C as an additional lipid target.

Reviewer's Comments: Even with well-treated LDL-C, some patients will have future CAD events. This study suggests there may be a role for non–HDL-C and TG in risk assessment beyond LDL-C. While there are not yet robust data that treating these parameters to target levels will lower CAD risk, one might suspect that such risk reduction is likely, given the powerful impact of LDL-C lowering. Future guidelines may include easily measured parameters such as non–HDL-C. (Reviewer-Karen Stout, MD).

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Keywords: Coronary Artery Disease, Hyperlipidemia Risk Assessment

Print Tag: Refer to original journal article
Large-population observational studies suggest that long-term statin (>1 year) use may help reduce the risk of gallstone disease with cholecystectomy.

**Background:** Statins reduce cholesterol biosynthesis in the liver, which may, in turn, decrease biliary cholesterol secretion. Since 80% to 90% of gallstones are formed from cholesterol-supersaturated bile, statins could potentially lower the risk for forming cholesterol stones, thereby reducing the risk of related complications or procedures, including cholecystectomy.

**Objective:** The authors analyzed data from a large research database to determine if a causal link could be established between statin use and the incidence of gallstones and cholecystectomy.

**Methods:** The UK-based General Practice Research Database was reviewed for patients with cholecystectomy between 1994 and 2008. Four controls were then identified and matched with each patient by age, gender, general practice, and time in the database. The use of lipid-lowering agents was recorded, included duration, dosage, and timing of use compared with incident cholecystectomy. The study population was further stratified into body mass index (BMI) classes, and findings were adjusted for smoking, ischemic heart disease, stroke, and estrogen use.

**Results:** 27,035 patients were identified with cholecystectomy during the study period, along with 106,531 matched controls. Of these subjects, 76% were women, and the mean age was 53.4 years. As expected, the risk of gallstone disease with cholecystectomy was strongly correlated with estrogen use and increasing BMI; 2396 patients (8.8%) and 8868 controls (8.3%) had documented statin use. The adjusted odds ratio of developing gallstones with cholecystectomy for the current statin use group was 0.78 (95% CI, 0.73 to 0.83) compared with the non-user group. Patients appeared to have the lowest risk after taking statins for >1 to 1.5 years. No significant benefit was seen with other lipid-lowering agents; in fact a slightly increased risk was noted with fibrate use. Individual statins and doses did not affect findings.

**Conclusions:** This observational study suggests that long-term (>1 year) statin use may reduce the risk of gallstone disease followed by cholecystectomy.

**Reviewer's Comments:** This observational study of a large British population shows similar findings compared to the analysis from the Nurses' Health Study published in the May 2009 issue of *Gastroenterology*. The authors also found that gallstone and cholecystectomy risk appeared independent of cholesterol level or cardiovascular disease. Limitations noted include the usual caveats inherent in population database analyses (ie, disease classification). In addition, lifestyle parameters relevant to gallstone development were not adjusted for. However, patients with higher BMIs were noted to derive the most benefit from statin use. Of the total population of patients with documented cholecystectomy, a relatively small proportion (approximately 8% or 2395 patients) actually took statins. A prospective study would help further define whether patients should be advised of this potential benefit when statins are needed for other indications, such as cardiovascular risk reduction. Or perhaps we would find that statins could be prescribed for protection against development of gallstone disease, independent of other indications. (Reviewer-Emily Y. Wong, MD).

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**Keywords:** Gallstone Disease, Cholesterol, Cholecystectomy, Statins

**Print Tag:** Refer to original journal article
Using A1C ≥6.5% to diagnose diabetes would lead to the same classification of diabetes as fasting glucose ≥126 mg/dL for 98% of U.S. adults.

Background: In June 2009, an International Expert Committee recommended the use of A1C to diagnose diabetes mellitus (DM). Based on the superior laboratory characteristics of A1C (ie, reproducibility, stability at room temperature) and data outlining A1C as more predictable of retinopathy than other diagnostic tests, the committee recommended A1C ≥6.5% as the test of choice for DM diagnosis. Previous criteria of fasting plasma glucose ≥126 mg/dL (≥7.0 mmol/L) and 2-hour post-oral glucose tolerance test (OGTT) plasma glucose ≥200 mg/dL (>11.1 mmol/L) were recommended as alternative options.

Objective: To compare A1C ≥6.5% and fasting plasma glucose ≥126 mg/dL for the identification of undiagnosed DM.

Design/Participants: Retrospective, longitudinal cohort study of 6890 adult participants in the U.S. National Health and Nutrition Examination Survey (NHANES) without self-reported DM and with data available for fasting AM plasma glucose and A1C.

Methods: Participants were categorized into 1 of 4 mutually exclusive groups based on the presence or absence of A1C ≥6.5% and fasting plasma glucose ≥126 mg/dL.

Results: The prevalence of undiagnosed DM was 2.3% using A1C for diagnosis and 3.6% using fasting glucose. Moderate agreement existed for diagnosis by A1C and fasting glucose (kappa, 0.60), with 95.9% of persons classified as not having DM by both tests and 1.8% classified as having DM by both tests. Diagnosis was discordant in 0.5% of participants with A1C ≥6.5% and fasting plasma glucose <126 mg/dL and in 1.8% of participants with A1C <6.5% and fasting plasma glucose ≥126 mg/dL. When fasting glucose was used as the gold standard, the sensitivity of A1C ≥6.5% was 49.9%, and the specificity was 99.5%.

Conclusions: The 2009 recommendations by the International Expert Committee to use A1C to diagnose DM would lead to the same classification of DM as fasting glucose for 97.7% of U.S. adults.

Reviewer's Comments: The lack of complete concordance between A1C and fasting glucose levels to diagnose DM is likely because these 2 measurements assess different aspects of glucose metabolism. The International Expert Committee recommends assessment for DM and confirmation of DM with the same test (ie, if A1C is elevated, confirm with A1C rather than fasting glucose or OGTT). The committee also recommends making a DM diagnosis if any of the accepted tests for DM diagnosis are elevated. In patients whose A1C or fasting glucose results are near the determined cutoffs for the diagnosis of DM but do not cross the threshold, recall that the risks for DM complications occur on a continuum, and there is no clear point at which risks for complications begin. Therefore, persons with elevated levels, even if not above suggested thresholds, should be counseled and treated with proven preventive strategies. Also remember that hemoglobin traits (eg, HbS) and any condition that causes changes in red cell turnover (eg, hemolytic anemia) can lead to spurious A1C results. (Reviewer-Melissa Hagman, MD).

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Keywords: A1C, Fasting Glucose, Diabetes, Diagnosis

Print Tag: Refer to original journal article
A practical, primary care-based weight loss program resulted in sustained weight loss of at least 5% in those who continued to participate at 2 years.

**Background:** Extreme obesity, defined as a body mass index (BMI) of >40, is often an indication for bariatric surgery. However, many patients lack the funding, social support, or general health to go through with bariatric surgery. Is a primary-care based weight loss program of any use in extreme obesity?

**Objective:** To determine whether real-life primary care practices could deliver a weight loss program for their extremely obese patients that resulted in significant and sustained weight loss.

**Design:** "Pragmatic" randomized, controlled trial.

**Participants:** 390 Louisiana patients with a BMI of 40 to 60 kg/m2.

**Methods:** This study was proposed and supported by the Louisiana Office of Group Benefits, which insures >100,000 state employees and dependents. Researchers hoped to design a "pragmatic" clinical trial, which would reflect real-life practice, by enrolling a diverse group of patients at multiple clinical sites. Eight clinical sites (7 family medicine clinics and an academic research center) in 8 cities were chosen for the study. Providers at each site received one 8-hour and one 6-hour training session covering pharmacotherapy, behavioral therapy, group therapy, and diets. Patients were randomized to usual care (referral to the Mayo Clinic Weight Management Website and annual visits) versus intensive medical intervention (IMI). This consisted of a 900-calorie liquid diet for up to 12 weeks followed by 4 months of a structured 1200 to 1600 kcal/day diet, 1 of 3 weight loss medications, and weekly to biweekly 1-hour small group behavior change sessions. In months 8 to 24, participants continued weight loss medications and monthly small group sessions. The liquid diet could be repeated for 4 to 12 weeks at a time as needed.

**Results:** The intention-to-treat analysis showed the mean weight loss for the usual-care group was 0% compared to 4.9% for the IMI group. About half of the subjects in each group had dropped out by 2 years. When the analysis was limited to those still attending the clinics and groups ("completers"), the mean weight loss was 9.7% for IMI versus 0.4% for usual care; 61% of the IMI "completers" maintained at least a 5% weight loss by the end of the study, and 14% maintained a 20% weight loss.

**Conclusions:** Primary care providers can effectively treat extreme obesity, although, for the majority of patients, the results do not match those expected with weight loss surgery.

**Reviewer's Comments:** A meta-analysis of bariatric surgery studies showed that, on average, expected long-term weight loss is 20 to 30 kg. The results of this study are less impressive but still clinically significant. For the many extremely obese patients who are not candidates for bariatric surgery, pragmatic, primary care-based weight loss programs could have a meaningful impact. (Reviewer-Karen A. McDonough, MD).

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Keywords: Extreme Obesity, Weight Loss

Print Tag: Refer to original journal article
Do Omega-3-Acid Ethyl Esters Help Achieve Lipid Targets?

*Effects of Prescription Omega-3-Acid Ethyl Esters on Non–High-Density Lipoprotein Cholesterol When Coadministered With Escalating Doses of Atorvastatin.*

Bays HE, McKenney J, et al:

Mayo Clin Proc 2010; 85 (February): 122-128

In patients with elevated non-HDL cholesterol, the addition of an omega-3-acid ethyl ester to statin therapy can increase HDL and lower triglycerides.

**Background:** Current recommendations target low-density lipoprotein (LDL) as the primary goal of lipid-lowering therapy. In patients with elevated triglycerides, secondary goals for non–high-density lipoprotein (non-HDL) are recommended. Prescription omega-3-acid ethyl esters (P-OM3) such as Lovaza have been effective in lowering triglycerides.

**Objective:** To determine the impact of adding P-OM3 to escalating doses of a statin on non–HDL-C and other lipid parameters.

**Design:** Randomized, double-blind, placebo-controlled study.

**Participants:** Men and women between the ages of 18 and 79 years with non–HDL-C >160 mg/dL and triglycerides between 250 and 599 mg/dL were eligible.

**Methods:** All patients underwent a 4-week lead-in, during which lipid-altering medications were discontinued. Participants were randomized to receive P-OM3 4 g/day for 16 weeks or a matching placebo. All participants received open-label atorvastatin 10 mg for the first 8 weeks, followed by 20 mg for 4 weeks and 40 mg for 4 weeks. The primary end point was the percent change in non–HDL-C between baseline and week 8. Other secondary end points included changes from baseline in total cholesterol, HDL-C, LDL-C, and triglycerides at weeks 12 and 16.

**Results:** 245 participants were randomized. Average age was 56 years, and average body mass index was 30; 56% were men, and approximately 90% were white. At baseline, total cholesterol was approximately 250 mg/dL, HDL-C was 37 mg/dL, LDL-C was 140 to 146 mg/dL, and triglycerides were 315 to 348 mg/dL. At 8 weeks, in the P-OM3 group, the non–HDL-C had decreased 40% (from 213 to 133 mg/dL) compared to 34% with atorvastatin alone (215 to 142 mg/dL). At both 12 and 16 weeks, the non–HDL-C was significantly lower in the P-OM3 group. At 16 weeks, the combination of P-OM3 and atorvastatin did not affect LDL-C compared to placebo, but HDL-C was 6% higher and triglycerides were 19% lower. In the post-hoc analysis, there were no significant differences in the rates of achieving lipid targets. Comparing the P-OM3 group to placebo, 86% versus 92% achieved their LDL-C target, and 89% versus 88% achieved their non–HDL-C target. Adverse effects were rare.

**Conclusions:** The addition of a P-OM3 to atorvastatin did reduce the non–HDL-C compared to atorvastatin alone. However, in the group studied, the majority of subjects met both their LDL-C and non–HDL-C goals with atorvastatin alone.

**Reviewer's Comments:** In this industry-sponsored study, the role of an omega-3-acid ethyl ester (Lovaza) in improving the non–HDL-C was examined. Certainly, the addition of the P-OM3 did show modest improvements in HDL-C and triglycerides. However, nearly all patients met their lipid goals on a statin alone. Therefore, until there are more clinical data on the efficacy of P-OM3 therapy (and other omega-3 products), I will continue to use them primarily for severe hypertriglyceridemia, and consider them when the non–HDL-C goal is not met with statin treatment. (Reviewer-Mark E. Pasanen, MD).

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**Keywords:** Statins, Omega-3-Acid Ethyl Esters, Hyperlipidemia, Hypercholesterolemia, Non-HDL

**Print Tag:** Refer to original journal article
More Data Support Increased Mortality With Low A1C in Type 2 Diabetes

Survival as a Function of HbA1c in People With Type 2 Diabetes: A Retrospective Cohort Study.
Currie CJ, Peters JR, et al:

Lancet 2010; 375 (February 6): 481-489

In a large cohort of diabetic patients, the lowest mortality was found with an A1C of 7.5%.

Background: The ideal hemoglobin A1C for patients with type 2 diabetes is controversial. Recent studies have suggested increased mortality with low hemoglobin A1C.

Design: Retrospective cohort study.
Participants: 47,970 patients in the United Kingdom who had their diabetes regimen intensified between November 1986 and November 2008. Patients were divided into 2 groups: cohort 1, in which patients had been treated with combination oral therapy (either adding metformin to a sulfonylurea or vice versa), or cohort 2, in which patients had been started on insulin.

Methods: The 2 cohorts were stratified into 10 groups based on the patient's average hemoglobin A1C for the remainder of the study period. These deciles ranged from an average A1C of 6.38% in the lowest decile up to 10.56% in the highest. The primary end point of the study was all-cause mortality.

Results/Conclusions: In both groups, mortality was lowest with an average hemoglobin A1C of 7.5. In the oral agent cohort, the hazard ratio for mortality was 1.3 in the lowest decile compared to 7.5%, and was 1.93 in the highest. In the insulin cohort, it was 1.79 in the lowest and 1.80 in the highest.

Reviewer's Comments: This study adds additional data to the discussion of target hemoglobin A1C in type 2 diabetics. I like that its findings make some intuitive sense: if the excess mortality in the low A1C group is related to hypoglycemia, it follows that insulin would be higher risk than oral agents. It may also reflect that the insulin-treated group had more severe disease or more co-morbidities. Combining this with the United Kingdom Prospective Diabetes Study results, it suggests that, with younger patients who are early in their illness, it may make sense to go for a low A1C, particularly if one can get there with an insulin sensitizer that has a low risk of hypoglycemia. As patients get older and develop other co-morbid conditions, it may be reasonable to allow a slightly higher A1C to avoid complications of overtreatment, especially if it seems like diabetes may not be the patient's life-limiting illness. I expect we will see continued debate and continued studies on this issue given the conflict in the current literature. (Reviewer-Christopher L. Knight, MD).

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Keywords: Diabetes

Print Tag: Refer to original journal article
Acyclovir -- Disappointing in Prevention of HIV Transmission

Acyclovir and Transmission of HIV-1 From Persons Infected with HIV-1 and HSV-2.
Celum C, Wald A, et al:


Daily suppressive acyclovir does not reduce HIV transmission by those co-infected by HIV and HSV-2.

Background: Most people infected by HIV are also infected with HSV-2. HSV reactivation is associated with higher HIV levels in blood and genital secretions, and symptomatic genital ulcers increase the risk of HIV transmission.

Objective: To determine whether suppression of HSV-2 reactivation with chronic acyclovir therapy would decrease the risk of transmission of HIV.

Design: Randomized, placebo-controlled trial.

Participants: 3408 couples discordant for HIV infection at 14 sites in Africa; 68% of the HIV-infected partners were women.

Methods: Stable couples in which only one partner was infected with HIV were recruited at 14 sites in southern and east Africa. The HIV-infected partner had to have a CD4 count of ≥250, have no AIDS-related illnesses, and be on no antiretroviral therapy. Persistent genital ulcers, ongoing acyclovir use, and pregnancy were also exclusion criteria. The HIV-infected partners were randomized to acyclovir 400 mg twice a day versus placebo, distributed at monthly visits for up to 24 months. Adherence, high-risk sexual activity, and symptoms of genital herpes were assessed monthly. Patients with ulcers were given open-label acyclovir for 5 days in addition to the study drug.

Results: The 2 groups were similar at baseline; 76% of the couples were married, and 90% lived together. The partners had a mean of 6 sexual contacts in the month before enrollment. Pill counts showed that adherence was excellent, and acyclovir patients had lower HIV viral loads and 73% fewer outbreaks of genital ulcers. One hundred and thirty-two uninfected partners had HIV seroconversion; however, in 38 cases, the HIV virus was not genetically linked to the partner's strain, suggesting transmission from someone else. Acyclovir did not have a significant effect on the likelihood of HIV transmission (HR with acyclovir, 0.92).

Conclusions: Acyclovir suppression of HSV-2 did not reduce HIV transmission, despite a reduction in HIV viral load and in genital ulcers.

Reviewer's Comments: This is a disappointingly negative study of a cheap and well-tolerated idea for preventing HIV transmission. The acyclovir was certainly effective in preventing herpes outbreaks, but patients should not be reassured that this makes them any less infectious. (Reviewer-Karen A. McDonough, MD).

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Keywords: Herpes Simplex Virus, HIV

Print Tag: Refer to original journal article
Can S. aureus Eradication Reduce Hospital Infections?

Preventing Surgical-Site Infections in Nasal Carriers of Staphylococcus aureus.

Bode LGM, Kluytmans JAJW, et al:


In nasal carriers of Staphylococcus aureus undergoing surgery, an aggressive eradication program reduces surgical site infections.

**Background:** Hospital-associated Staphylococcus aureus infections are a significant cause of morbidity. Previous efforts, including in nasal carriers, to decrease hospital infection rates have been inconsistent.

**Objective:** To determine if an approach incorporating total body wash and nares treatment would decrease S. aureus hospital-associated infections in nasal carriers.

**Design:** Double-blind, placebo-controlled, randomized trial.

**Participants:** Patients aged ≥18 years admitted to internal medicine or surgical wards with an expected hospital stay of at least 4 days were eligible. Exclusion criteria included the presence of an active S. aureus infection, pregnancy/breast feeding, and/or the use of mupirocin in the previous 4 weeks.

**Methods:** To identify nasal carriers of S. aureus, a rapid polymerase chain reaction assay was performed on nasal swabs at the time of admission. Patients who tested positive for S. aureus were randomized to an eradication regimen or placebo. The eradication regimen consisted of nasal mupirocin ointment twice daily and a total body wash with chlorhexidine soap daily for 5 days. In the placebo arm, patients received matched ointment and soap but without active ingredients. The primary outcome was the cumulative incidence of hospital-associated S. aureus infections. Another end point of interest was length of hospitalization.

**Results:** In >6700 patients screened, 1270 samples tested positive for S. aureus (18.8%). The average age of these patients was approximately 62 years, and the majority of patients were on surgical services (88%). The rate of S. aureus hospital-associated infections was lower in the treatment group, 3.4% versus 7.7%. Most notable was the reduction seen in deep surgical site infections, 0.9% versus 4.4%. When strains were tested, most of the reduction in S. aureus infections was in endogenous infection (as opposed to exposure to a new strain). The mean duration of hospitalization was lower in the treatment group, 12.2 versus 14.0 days.

**Conclusions:** In nasal carriers of S. aureus admitted to the hospital with an expected stay of at least 4 days, treatment with total body washes of chlorhexidine and nasal mupirocin significantly decreased the rate of surgical site infections and reduced the length of hospitalization.

**Reviewer’s Comments:** This study offers hope as we battle hospital-associated infections. It shows that an aggressive eradication regimen, in this case with total body wash and nasal treatment, can decrease infection rates. This was limited to higher-risk situations (in which hospitalization was expected to be prolonged) and utilized a rapid test to identify the carriers. Although all S. aureus strains were sensitive to methicillin, as most S. aureus strains in the United States are mupirocin-sensitive, it is likely that similar results could be obtained with resistant S. aureus. The authors point out that approximately 250 patients would need to be screened to prevent one infection and 23 carriers would need to be treated to prevent one infection. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Staphylococcus aureus, Hospital-Acquired Infections

Print Tag: Refer to original journal article
Measuring procalcitonin levels can help reduce antibiotic use in patients with lower respiratory tract infections.

**Background:** In patients presenting to the emergency department (ED) with symptoms suggesting bronchitis or pneumonia, it can be difficult to determine who needs antibiotics and for how long.

**Objective:** To assess outcomes when procalcitonin is used to guide antibiotic therapy in lower respiratory tract infections.

**Design:** Multi-center, randomized, controlled trial.

**Participants:** 1359 patients presenting with a lower respiratory infection to 1 of 6 EDs in Switzerland.

**Methods:** Patients were randomized at study entry into either usual care or procalcitonin groups. Patients in the procalcitonin group had procalcitonin levels measured at study entry. Results were typically available within 1 hour on the study website, which provided both results and a treatment recommendation for antibiotics based on a study algorithm. Depending on the procalcitonin level, the antibiotic recommendation might have been "strongly discourage," "discourage," "encourage," or "strongly encourage." In patients who were receiving antibiotics, procalcitonin levels were repeated on days 3, 5, and 7 and at discharge; for patients who either had a dramatic decrease in procalcitonin or whose procalcitonin dropped below a low threshold value, the algorithm recommended stopping antibiotics.

**Results:** The investigators analyzed results from a total of 1359 patients (community-acquired pneumonia in 68%, COPD exacerbations in 17%, acute bronchitis in 11%, and no lower respiratory tract infection in 4%). Initial rates of antibiotic prescription decreased: community-acquired pneumonia prescriptions were nearly 100% in the control group and 91% in the procalcitonin group, whereas antibiotic prescriptions for acute bronchitis decreased from 50% to 23% in the procalcitonin group. On average, the duration of IV antibiotic therapy decreased from 3.8 to 3.2 days, and oral antibiotic duration decreased from 4.9 to 2.5 days. The procalcitonin group also showed a decrease in adverse effects, from 28% to 20% (primarily nausea, diarrhea, and rash).

**Reviewer's Comments:** This is an important study. All kind of good things can come from reducing antibiotic use: reduced rates of resistance, fewer adverse effects, and perhaps even lower costs. Procalcitonin appears to be a helpful marker for bacterial infection that may reduce antibiotic use when used as an aid in decision making. (Reviewer-Christopher L. Knight, MD).

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Keywords: Pneumonia, Bronchitis, Procalcitonin

Print Tag: Refer to original journal article
Is Procalcitonin Effective in the ICU?

*Use of Procalcitonin to Reduce Patients' Exposure to Antibiotics in Intensive Care Units (PRORATA Trial): A Multicentre Randomised Controlled Trial.*

Bouadma L, Luyt C-E, et al:

Lancet 2010; 375 (February 6): 463-474

Monitoring procalcitonin levels can help reduce antibiotic use in the ICU.

**Background:** Antibiotics are frequently used in the ICU, but selection of patients and duration of therapy are sometimes unclear.

**Objective:** To assess the outcomes of using procalcitonin to manage antibiotics in critically ill patients.

**Design:** Multi-center, randomized, controlled trial.

**Participants:** 630 patients in 8 ICUs in France.

**Methods:** Patients were randomized at study entry into either usual care or procalcitonin groups. Patients in the procalcitonin group had procalcitonin levels measured at study entry. Depending on the procalcitonin level, the antibiotic recommendation might have been "strongly discourage," "discourage," "encourage," or "strongly encourage." If patients were hospitalized, they had repeat procalcitonin levels after admission, which were used to guide duration of antibiotics. The significant difference in the procalcitonin group was in antibiotic exposure. On average, 14.3 days of the hospital stay in these patients were spent without antibiotics, compared to 11.6 days in the control group; stated otherwise, on average, the procalcitonin group received antibiotics for 65% of their hospital stay, and the control group for 81%. Perhaps as important as the differences between groups were the areas in which no difference was found. Mortality, relapse rate, length of stay in the ICU and the hospital, and number of days without mechanical ventilation all showed no significant differences.

**Reviewer's Comments:** Procalcitonin reduces antibiotic use in the ICU and has also been shown to reduce both initial prescriptions and duration of therapy in lower respiratory tract infections, all without changing outcomes. Procalcitonin is certainly a promising addition to clinical decision making. Although it's probably not ready for prime time, I anticipate it will become more commonly used in the next several years. (Reviewer-Christopher L. Knight, MD).

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Keywords: Sepsis, Intensive Care, Antibiotics, Procalcitonin

Print Tag: Refer to original journal article
Acupuncture Is Reasonable Alternative for Treating Hot Flashes

Acupuncture Versus Venlafaxine for the Management of Vasomotor Symptoms in Patients With Hormone Receptor-Positive Breast Cancer: A Randomized Controlled Trial.

Walker EM, Rodriguez AI, et al:

J Clin Oncol 2010; 28 (February 1): 634-640

Acupuncture represents a possible alternative to venlafaxine in the treatment of hot flashes related to estrogen antagonist therapy.

**Background:** Women with breast cancer often suffer from hot flashes during the hormone-modulating therapy phase of treatment, which usually continues for at least 5 years after initial treatment with surgery, chemotherapy, and/or radiation. Venlafaxine has been shown to be effective in reducing hot flashes, but patients may be reluctant to take another medication, in part due to side effects. Acupuncture has been shown to help reduce menopausal hot flashes in a number of small studies.

**Objective:** To compare the effects of acupuncture with venlafaxine in treating vasomotor hot flashes.

**Design:** Randomized, controlled trial.

**Participants/Methods:** 50 women were randomized to receive either 12 weeks of acupuncture or venlafaxine treatment and were then observed for 1 year. Patients had completed surgery or chemotherapy for breast cancer and were taking either tamoxifen or Amridex hormonal therapy. The acupuncture group received 2 treatments per week for 4 weeks, then once a week for 8 weeks, at standardized acupoints, with limited variation allowed per study protocol. Patients in the venlafaxine group received 37.5 mg at night for 1 week, which was increased to 75 mg at night as tolerated for the remaining 11 weeks.

**Results:** Both the venlafaxine and acupuncture groups experienced at least 50% improvement in hot flash frequency during the treatment period. Hot flashes recurred within 2 weeks of stopping venlafaxine treatment, but not in the acupuncture group ($P<0.001$). Adverse effects reported with venlafaxine included nausea, dry mouth, anxiety and dizziness. Acupuncture patients had no reported adverse effects, but incidental benefits included improved clarity of thought, libido, and sense of well-being.

**Conclusions:** Acupuncture is at least as effective as venlafaxine in treating hot flashes in women on hormone-modulating therapy after breast cancer treatment, with fewer side effects and possible longer sustained benefit.

**Reviewer's Comments:** This small study confirms in part findings from other small studies in Europe looking at acupuncture for treating hot flashes in this population. Acupuncture has been shown to be an effective adjuvant treatment for nausea and pain in cancer patients, but results have been mixed in treating postmenopausal hot flashes in the general population. In addition to the study size and poor follow-up, this study design was limited by use of the venlafaxine arm as the control. A placebo drug arm may have helped determine the natural history of hot flashes in this population, and/or a sham acupuncture arm would have blinded study participants. Interestingly, of the 143 patients eligible to participate in the study, 30 declined because of reluctance to be randomly assigned to receive venlafaxine, but none declined because of acupuncture. However, despite the difficulty of conducting clinical trials in this setting, these data do help to confirm the validity of acupuncture as a reasonable alternative to medication in treating hot flashes. (Reviewer-Emily Y. Wong, MD).

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Keywords: Menopause, Hot Flashes, Acupuncture, Breast Cancer

Print Tag: Refer to original journal article
Conventional Pap testing performs as accurately as liquid-based cytology for identification of cervical cancer precursors.

**Background:** Liquid-based cytology represents a considerable investment in support infrastructure, promising fewer unsatisfactory samples and opportunity for additional testing such as reflex human papillomavirus (HPV) testing. Conventional cytology may be more affordable and accessible in rural and underserved communities both in the U.S. and in developing countries.

**Objective:** To test the performance of liquid-based cytology compared with conventional cytology in terms of detection of histologically confirmed cervical intraepithelial neoplasia (CIN).

**Methods:** 89,784 women in 246 family practices were cluster randomized to either conventional Papanicolaou (Pap) test or liquid-based cytology as part of the Dutch cervical cancer screening program between April 2004 and July 2006. Cervical histology served as the gold-standard test for CIN. The main outcome was comparison of performance between the 2 diagnostic tests as expressed by the detection rates (DRs) of histologically confirmed CIN or cervical carcinoma. Gynecologists, pathologists, cytotechnologists, and other staff involved in follow-up and review were blinded to the screening system used.

**Results:** Detection rates were comparable between the 2 screening methodologies at each level of histological outcome. Thus, liquid-based cytology was found to be comparable in accuracy to conventional Pap cytology whether the histological outcome was CIN grade 1, 2, 3 or cervical carcinoma. Positive predictive values were also found to be highly correlated between the 2 methods in identifying dysplastic findings such as atypical cells of unknown significance (ASCUS), atypical glandular cells (AGUS), low-grade squamous intraepithelial lesion (LGSIL), or high-grade squamous intraepithelial lesion (HGSIL). A slightly lower "unsatisfactory" rate was noted for liquid-based testing, but reported rates were already very low.

**Conclusions:** Conventional Pap testing appears to be just as accurate as liquid-based cytology in terms of relative sensitivity and positive predictive value for detection of cervical cancer precursors.

**Reviewer’s Comments:** This large, randomized, controlled trial validates the continued use of conventional Pap testing technology as compared with the newer liquid-based method in terms of cytological diagnosis. However, the option for reflexive HPV typing in liquid specimens remains attractive. Most U.S. urban health-care practices and laboratories have already moved to the more expensive liquid-based testing, yet some would argue that routine cytological testing may become obsolete in the next decade. Other recent advances in cervical cancer prevention include expensive vaccines targeting high-risk HPV types in developed countries and low-cost self-administered HPV testing in developing countries. As health-care resources become scarcer on a global scale, we must ask ourselves if newer technologies always offer better value for the health-care dollar. (Reviewer-Emily Y. Wong, MD).

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**Keywords:** Cervical Cancer Screening, Pap Testing, Prevention, Liquid-Based Cytology, Dysplasia

**Print Tag:** Refer to original journal article
Urinary incontinence is often undiagnosed in the clinical setting, despite adequate access to care.

**Background:** Urinary incontinence has a significant impact on quality of life, yet reported prevalence likely underestimates actual prevalence, as a number of barriers to communication prevent women from receiving appropriate care.

**Objective:** To better characterize the burden of undiagnosed urinary incontinence by surveying a population of managed care patients.

**Participants/Methods:** The eligible population for this study included 115,117 women aged 25 to 80 years enrolled in the Kaiser Permanente Northwest plan from January 1998 to May 2002. A questionnaire was developed detailing duration, frequency and amount of urinary leakage, nature of symptom onset (stress, urge, or mixed), and quality of life. The survey was mailed to a random sample of 2118 women. Of the women who reported moderate or severe incontinence, a further chart review was conducted to identify potential documented evidence for discussion or treatment of urinary incontinence in the 12 months prior to the survey completion date.

**Results:** 875 women completed the questionnaire, yielding a response rate of 41%. Of these women, 461 patients (52.6%) were noted to have had urinary incontinence in the past 12 months, while 340 (38.9%) had had symptoms in the past 7 days. When adjusted for age, the prevalence of undiagnosed incontinence was 51% in the past 12 months and 38% for the past 7 days. Younger women tended to have stress incontinence and older women were more likely to have mixed or urge incontinence. Severity of incontinence was measured by the Sandvik Severity Index, which incorporates frequency and amount of leakage. Symptom severity was correlated with worse quality of life. A total of 234 women had moderate to severe symptoms; of these, only 11 women (4.7%) had documentation of urinary incontinence in the medical record, despite 4 median office contacts and 2 median telephone contacts.

**Conclusions:** Urinary incontinence is a largely unrecognized and untreated condition in women, with potential for considerable impact on quality of life.

**Reviewer's Comments:** This study validates previous reports that identify a number of barriers to care for urinary incontinence, including fear of medical intervention, legitimacy of symptoms as medical problems, and embarrassment surrounding the condition. This survey was limited in its response rate of 41%, as it is unclear if a selection bias may have been introduced. For example, nonresponders may have chosen not to respond despite symptoms, or they may not have had symptoms, leaving them less motivated to participate. However, responses did suggest significant impact of symptom severity on quality of life, and apparently significant underreporting of symptoms to care providers despite multiple episodes of care. Incontinence in older populations may be associated with depression, decreased mobility, and even institutionalization. Awareness of this underreported condition may help prompt earlier care and relatively simple interventions. (Reviewer-Emily Y. Wong, MD).

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Keywords: Undiagnosed Urinary Incontinence, Prevalence, Severity, Reporting

Print Tag: Refer to original journal article
Can Estrogen-Modulating Drugs Be Used for Primary Prevention of Breast Ca?

Systematic Review: Comparative Effectiveness of Medications to Reduce Risk for Primary Breast Cancer.
Nelson HD, Fu R, et al:

Tamoxifen, raloxifene, and tibolone are effective in reducing the risk for invasive breast cancer, but are also associated with significant risks, serious adverse events, and bothersome side effects.

**Background:** Estrogen-modulating drugs have proven effectiveness as an adjunctive therapy to reduce the risk for recurrent breast cancer. A number of studies have more recently posed the question of whether or not they can be used for primary prevention of breast cancer.

**Objective:** To conduct a systematic review comparing how effective estrogen-modulating medications are in reducing the risk for primary breast cancer.

**Methods:** Standard methodology was followed in selection of studies to be included in the systematic review. Studies were required to have treatment durations of ≥3 months and to have enrolled ≥100 participants in order to be included. Drugs studied included 2 selective estrogen modulators (SERMs), tamoxifen and raloxifene, and the selective tissue estrogenic activity regulator, tibolone. Only double-blind, placebo-controlled or head-to-head randomized, controlled trials enrolling women without preexisting breast cancer were included. Two independent investigators used predefined criteria to assess the quality of evidence.

**Results:** 14 articles from 6 trials were selected from 4230 abstracts and 58 full-text articles. Four placebo-controlled trials found that tamoxifen reduced the risk of invasive breast cancer. Similar findings were seen in 2 raloxifene trials and 1 tibolone trial. Overall, approximately 7 to 10 cases of invasive breast cancer would be reduced per 1000 women per year, assuming 5 years of use. The risk of estrogen receptor-negative invasive breast cancer and noninvasive breast cancer was not reduced. Thromboembolic risk was increased: slightly higher with tamoxifen compared with raloxifene, with an overall risk of 4 to 7 per 1000 women per year. Increased risk for endometrial cancer and cataracts was associated with tamoxifen. Tibolone showed increased risk for stroke. Common adverse event effects included hot flashes, genitourinary complaints, vaginal bleeding, and musculoskeletal symptoms. All 3 drugs also reduced fracture risk.

**Conclusions:** Tamoxifen, raloxifene, and tibolone are effective in reducing the risk for invasive breast cancer, but are also associated with significant risks of serious adverse events and bothersome side effects.

**Reviewer’s Comments:** This meticulously conducted systematic review and meta-analysis helps us by validating medications that can reduce the risk for breast cancer under specific circumstances. However, there are also significant risks to be considered, including potentially life-threatening and disabling events related to thromboembolic disease, endometrial cancer, and stroke. In addition, while these drugs can prevent estrogen receptor-positive breast cancer, they are not effective in nonreceptor-positive disease. Tamoxifen and raloxifene were found to have similar protective effects for women irrespective of age, family history, menopause status, or history of estrogen use. While intuitively we might consider use of these medications for a select population for which the protective benefits might outweigh the risks, these studies are not helpful in defining such a population, and thus for now, I would encourage patients not to use these drugs for primary prevention of breast cancer. (Reviewer-Emily Y. Wong, MD).

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Keywords: Breast Cancer, Primary Prevention, Raloxifene, Tamoxifen, Tibolone

Print Tag: Refer to original journal article
Psychoactive Medications May Be Overused in Newly Admitted NH Patients

Provision of Psychopharmacological Services in Nursing Homes.
Molinari V, Chiriboga D, et al:

A majority of newly admitted NH patients receive new psychoactive medications within 3 months of admission despite no recent use of psychoactive medications or psychiatric diagnosis prior to admission.

**Background:** National legislative efforts dating back over 20 years aimed to reduce use of psychoactive medications and physical restraints among nursing home (NH) residents. **Objective:** To explore factors associated with the receipt of psychopharmacological care in newly admitted NH patients and to investigate the association between receiving psychopharmacological treatment and prior psychiatric diagnosis and treatment in the 6 months before NH admission. **Design:** Observational study over 1 calendar year (2003). **Participants:** 947 newly admitted, long-term care NH residents in the state of Florida who were Medicaid eligible and ≥65 years of age were included in the study. **Results:** The mean study patient age was 83 years; 74% were women, and 73% were white. Within 3 months of admission, 71% of residents were receiving at least 1 psychoactive medication. Over 15% of patients were on 4 or more medications. Twelve percent received nonpsychopharmacologic care. The rate of psychoactive medication use was similar among patients who did and did not have a prior psychiatric diagnosis. Sixty-four percent of residents on psychoactive medications within 3 months of admission did not have a history of psychoactive medication use in the preceding 6 months. Institutional size, location (rural vs urban), or profit status (profit, nonprofit, or government) was not associated with psychoactive medication use. Black residents were less likely to receive psychoactive medications than Whites or Hispanics. **Conclusions:** A majority of newly admitted NH residents received ≥1 psychoactive medication despite having neither prior recent psychopharmacological treatment nor a prior psychiatric diagnosis. **Reviewer’s Comments:** Despite the intention of the 1987 Omnibus Budget Reconciliation Act (OBRA) to reduce inappropriate psychoactive medication use and promote nonpharmacological approaches to mental health care in nursing homes, in the >20 years since OBRA’s passage, only modest changes in these areas have been noted. This study lacked details regarding the specific psychoactive drugs that were used and was not designed to identify if psychoactive medication use was appropriate or not. However, given the strikingly high rates of newly added psychoactive medications after NH admission, I suspect that a large percentage of new prescriptions were likely avoidable. Unfortunately, nursing homes in America still suffer from budgetary and staffing constraints that limit training and implementation of nonpharmacological approaches to behavioral problems. Further, psychiatric and counseling services are often limited or not available in many facilities. Whether you are a medical-care provider in the NH setting, a patient, or perhaps even a family member of yours is being newly admitted to a nursing facility, this study should serve to alert you to the high likelihood that new psychoactive medications will be added after admission. Careful scrutiny is advised to make sure that such orders are appropriate and necessary. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Nursing Home Patients, New Admission, Psychoactive Medications

Print Tag: Refer to original journal article
Caregivers of patients with late-life depression experience significant burden that can be lessened by effective treatment of the patient’s depression.

**Background:** The effect of late-life depression on family caregivers has not been well studied despite the relatively high prevalence of clinically significant depressive symptomatology in late life.

**Objective:** To evaluate the effects of treating late-life depression on burden of care experienced by family caregivers.

**Methods:** The current study was part of a larger clinical treatment trial of late-life depression. All study subjects received escitalopram 10 mg/day during a 6-week open treatment phase. Partial responders were then randomized to receive escitalopram 20 mg/day alone or in combination with weekly psychotherapy for 16 weeks.

**Participants:** Adults over age 60 participating in a treatment study for major depressive disorder (MDD) who also enrolled in an ancillary family caregiver study. Methods: The presence of MDD was diagnosed by standard DSM-IV criteria; in addition, all enrolled subjects had a Hamilton Rating Scale for Depression (HRSD) score of at least 17. A partial response was defined as an improvement in HRSD to a score of 11 to 14, and remission was defined as an HRSD score of ≤7 for 3 consecutive weeks. These end points were evaluated as predictors of changes in measures of caregiver general burden and caregiver depression-specific burden.

**Results:** The mean patient age was 73 years, 70% were women, and 89% were white. Roughly half of the caregivers were spouses and half were adult children of patients. At baseline, caregivers reported a moderate to high level of general caregiver burden. Improvement in depression during the open phase of the trial was associated with a significant decrease in depression-specific caregiver burden and a trend toward a lower general burden ($P = 0.08$). During the randomized phase of the study, improved patient depression scores were also associated with lower depression-specific caregiver burden. Caregivers of the roughly 50% of patients whose depression remitted during treatment reported significantly less caregiver burden relative to caregivers of patients who did not remit.

**Conclusions:** Treatment of late-life depression reduces measures of burden among family caregivers of depressed patients.

**Reviewer's Comments:** This study may well underestimate the potential benefit of depression treatment on reducing caregiver burden as the study cohort consisted of partial responders to initial therapy, a group that may be less likely to achieve a full remission even with continued treatment. Caregivers of persons with late-life depression may be at increased risk for adverse health outcomes related to the burden of their care giving. If caregivers collapse under the weight of that burden, then both they and the patient they are caring for will suffer. This study expands attention to caregivers of older persons with depression, and serves to remind practitioners that an important aspect of caring for frail older adults is to help support patient caregivers. Increased efforts to recognize and treat late-life depression may help both patients and their caregivers. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Late-Life Depression, Caregiver Burden

Print Tag: Refer to original journal article
One More Reason to Watch Your Weight

Being Overweight in Midlife Is Associated With Lower Cognitive Ability and Steeper Cognitive Decline in Late Life.

Dahl A, Hassing LB, et al:


Being overweight at midlife may adversely affect cognitive ability in late life.

Background: Substantial evidence indicates that being overweight at midlife is associated with increased risk for dementia in late life. Whether midlife measures of body mass index (BMI) are associated with changes in cognitive ability over extended longitudinal periods of time has not been well studied.

Objective: To examine the association between being overweight in midlife and changes in cognitive ability over time.

Design: Longitudinal cohort study 40 years in duration.


Methods: Baseline surveys in 1963 and 1973 included self-reported data on subjects’ height, weight, medical conditions, and lifestyle factors (education, smoking, and alcohol use). Overweight status was defined as having a BMI ≥25. Neuropsychological tests of cognitive abilities were performed every 3 years between 1986 and 2002. Patients were screened for incident dementia throughout the study period.

Results: 60% of the nearly 800 study participants were women, approximately one-half had a low level of education (≤6 years), and over half were present or ex-smokers. The mean age at midlife when initial BMI measures were obtained was 42 years. At midlife, the mean initial BMI was 24. Roughly 25% of the study sample had a BMI in the overweight range (BMI, 25 to 30), while 4% were obese (BMI, ≥30). Persons with higher BMIs in midlife had lower general cognitive ability in late life after adjusting for lifestyle factors and the presence of cardiovascular disease. Higher midlife BMI was also associated with faster declines in cognitive ability over time. Less than 10% of subjects were diagnosed with dementia during the study period, and the study findings did not change when these subjects were excluded from the analysis.

Conclusions: Being overweight at midlife is associated with a more rapid decline in cognitive ability over time and a lower general cognitive ability in late life.

Reviewer's Comments: Current evidence indicates that the adverse effects of being overweight extend to neurological dysfunction. This longitudinal study by Dahl and colleagues adds to the existing knowledge base by demonstrating that being overweight at midlife precedes the development of steeper cognitive decline and lower cognitive ability in late life. This effect was observed at even a modestly elevated BMI of >25. Obesity is associated with increased cardiovascular disease burden and increased inflammation, both of which are potential mechanistic explanations for the link between being overweight and cognitive dysfunction. Although this study has potentially significant flaws, including only very crude adjustments for lifestyle factors and no adjustments for physical activity level, it does provide 1 more reason we can give to patients to help motivate them in the ongoing battle against obesity. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Overweight, Midlife, Cognitive Decline

Print Tag: Refer to original journal article
Less Sedation May Lead to Less Delirium

Sedation Depth During Spinal Anesthesia and the Development of Postoperative Delirium in Elderly Patients Undergoing Hip Fracture Repair.


In elderly patients undergoing hip fracture surgery with spinal anesthesia, light sedation during surgery significantly reduces the incidence of postoperative delirium.

**Background:** In elderly patients undergoing surgery, the postoperative course is frequently complicated by delirium. Risk factors for postoperative delirium have been identified, but few are easily modified.

**Objective:** To determine if minimizing the degree of sedation while undergoing hip fracture surgery with spinal anesthesia decreases the incidence of postoperative delirium.

**Design:** Randomized, double-blind trial.

**Participants:** Patients ≥65 years of age undergoing hip fracture surgery with spinal anesthesia were eligible. Exclusion criteria included contraindications to spinal anesthesia, prior hip surgery, preoperative delirium, and severe dementia (as defined by a Mini-Mental Status Examination (MMSE) score of <15).

**Methods:** Patients were randomized to either light or deep sedation with propofol during their surgical procedure. The bispectral index (BSI), calculated from electroencephalogram tracings, was used to monitor the level of sedation. While in deep sedation, patients cannot respond to painful stimuli; while in light sedation, patients can respond to voice. Multiple other variables were collected, including analgesic use, pain scores, and blood pressures. The Confusion Assessment Method (CAM), a validated tool for identifying delirium, was used to assess for delirium each day. The primary outcome was the presence of delirium beginning on the second postoperative day through the remainder of the hospitalization.

**Results:** 114 patients were randomized, evenly split between deep and light sedation. The average age was 81 years, and the average MMSE was 25 (out of 30). The intraoperative experiences were similar in both groups, although the deep sedation group received higher doses of propofol, and the duration of surgery was slightly longer (93 minutes vs 79 minutes). As for the primary outcome, in patients receiving light sedation, delirium occurred much less frequently, 19% versus 40%. If delirium developed, however, the duration of the episodes was similar in both groups, lasting roughly 3 days. Other variables identified as predictive of postoperative delirium included preoperative dementia, units of red cells transfused, and admission to an ICU. Age, education level, duration of surgery, and total dose of propofol were not predictive.

**Conclusions:** In elderly patients undergoing hip fracture surgery with spinal anesthesia, light sedation during surgery significantly reduced the incidence of postoperative delirium.

**Reviewer’s Comments:** I have limited knowledge of what goes on in the operating room, and do not know how deeply my patients are sedated. However, I certainly see my share of postoperative delirium. As the authors point out, one episode of delirium could be prevented for every 4.7 patients treated with light sedation. Therefore, one can make a strong case for better understanding the norm for anesthetic sedation in your institution. As hip fracture management becomes more a partnership between internists and orthopedics, perhaps we should both be working closer with our colleagues in anesthesia to maximize patient outcomes. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Spinal Anesthesia, Delirium, Hip Fracture

Print Tag: Refer to original journal article
Oral fingolimod is a new treatment for multiple sclerosis that is more effective than interferon, but has important adverse events.

**Background:** Fingolimod is a sphingosine-1-phosphate–receptor modulating agent that has shown promise in the treatment of multiple sclerosis (MS). It limits lymphocytic release from secondary lymph tissue, thereby reducing circulation of lymphocytes to the central nervous system.

**Objective:** To compare fingolimod with interferon in the treatment of relapsing MS.

**Design:** Randomized, double-blind, double-dummy study.

**Participants:** Patients between 18 and 55 years of age with MS and a relapsing-remitting course were eligible, assuming at least 1 relapse in the last year or 2 in the past 2 years. Exclusion criteria included relapse in the prior month, active infection, or immunosuppressed state.

**Methods:** Patients were randomized for 12 months to either oral fingolimod at 0.5 mg or 1.25 mg daily, or interferon beta-1a 30 µg intramuscularly weekly. Disability scores were calculated every 3 months and MS functional scores every 6 months. MRI was performed at entry and at 12 months. Safety assessments were done monthly for the first 3 months and then every 3 months thereafter. The primary end point was the annualized relapse rate, while secondary end points included MRI progression and disability worsening.

**Results:** 1292 patients from 18 countries were randomized, 89% of whom completed the study. Average age was 36 years; approximately two-thirds were women and about half had been treated with interferon previously. The annual relapse rate was significantly lower in both fingolimod groups as compared to interferon. No relapse was reported in approximately 80% on fingolimod as compared to 69% for interferon. On MRI, there were fewer new or enlarged lesions with fingolimod, and MS functional and disability scores were statistically better. However, defined progression in disability was similar in all groups (with very low rates in all 3 groups). Two patients died in the fingolimod arm (both on the higher dose), 1 from disseminated varicella and another from herpes simplex encephalitis. Bradycardia and atrioventricular block, known effects of fingolimod, occurred in a small percentage. Neoplasms also occurred more frequently in the fingolimod groups, including melanoma, basal cell carcinoma, and breast cancer.

**Conclusions:** Oral fingolimod, a new potential treatment for MS, improved relapse rates and MRI progression as compared to interferon. However, serious adverse events were relatively common, and long-term safety will have to be monitored.

**Reviewer’s Comments:** This is 1 of 2 papers simultaneously published in the *New England Journal of Medicine* on fingolimod. The other was a placebo-controlled study with similar findings. An effective oral drug for MS would obviously be attractive, and fingolimod appears to be at least as good, if not better, than interferon in decreasing relapses. However, the serious adverse events should not be overlooked. As we monitor this new drug, we will need to keep a close eye on the cardiovascular and neoplastic effects. (Reviewer-Mark E. Pasanen, MD).
Systematic Review of Thromboprophylaxis in Acute Spinal Injuries

Thromboprophylaxis in Patients With Acute Spinal Injuries: An Evidence-Based Analysis.
Ploumis A, Ponnappan RK, et al:


This systematic review and meta-analysis of thromboprophylaxis following acute spinal injury demonstrated, most importantly, that LMWH is superior to UFH at preventing DVT.

Background: Venous thromboembolic events (VTE) are common following acute spinal injuries. The frequency of VTE, including deep venous thromboembolism (DVT) and pulmonary embolism (PE), is estimated to range from 67% to 100% in untreated patients with spinal cord injury in the first 3 months following injury. Although thromboprophylaxis is commonly used following spinal injury, it remains uncertain whether any regimen is superior.

Objective: To perform a systematic review and meta-analysis of the published literature on thromboprophylaxis following acute spinal injury.

Methods: Studies were selected from the MEDLINE, EMBASE, and Cochrane databases. Included studies compared methods of preventing thromboembolic events following acute spinal injury (with and without spinal cord injury). All included studies included at least 2 weeks of thromboprophylaxis and used standard objective measures of VTE and bleeding; studies assessing the efficacy and safety of thromboprophylaxis need not have been randomized trials to be included. A subset of studies that compared low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) for thromboprophylaxis were required to be randomized trials of at least 6 weeks duration. Meta-analyses were performed using software from the Cochrane Collaboration.

Results: 489 studies were identified by their search criteria, of which only 21 qualified for inclusion. DVT was significantly more common in patients with acute spinal trauma who sustained spinal cord injury compared with spinal trauma patients without spinal cord injury (odds ratio [OR], 6.0; 95% CI, 2.9 to 12.7). Only 1 study compared mechanical thromboprophylaxis with mixed mechanical and pharmacological thromboprophylaxis; this study did not show a significant difference between the 2 strategies. Four studies compared thromboprophylaxis with vitamin K antagonists (such as warfarin) with heparin-based regimens; no significant differences were seen. Five randomized trials compared LMWH and UFH in patients with acute spinal cord injury; LMWH was associated with a significantly lower risk of DVT compared with UFH (OR, 2.8; 95% CI, 1.4 to 5.7); no difference in bleeding was noted.

Conclusions: VTE was significantly more likely following acute spinal trauma with spinal cord injury compared to spinal trauma without spinal cord injury. LMWH was associated with a lower risk of DVT compared with UFH.

Reviewer's Comments: Hypercoagulability develops within hours of spinal cord injury and persists for up to 3 months, and it is common practice to initiate thromboprophylaxis early. Although there is a paucity of data, it is certainly prudent to initiate mechanical thromboprophylaxis promptly, as this is safe even in the setting of polytrauma and the perioperative period. The most important conclusion of this paper is that LMWH is superior to UFH for pharmacological thromboprophylaxis; this is also the most methodologically sound conclusion given the requirement for randomized trials for this portion of the review. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Acute Spinal Injuries, Thromboprophylaxis, Meta-Analysis

Print Tag: Refer to original journal article
St. John’s Wort Less Effective Than Placebo for IBS
A Randomized, Double-Blind, Placebo-Controlled Trial of St John's Wort for Treating Irritable Bowel Syndrome.
Saito YA, Rey E, et al:
Am J Gastroenterol 2010; 105 (January): 170-177

St. John’s wort is not effective for the treatment of irritable bowel syndrome.

Background: St. John's wort (SJW) has been shown to be effective in the treatment of mild-to-moderate depression perhaps in part due to effects on serotonin. Manipulation of serotonin and its receptors can alter gut function, and some treatment options for irritable bowel syndrome (IBS), such as selective serotonin reuptake inhibitors and serotonin receptor agonists, may act this way.

Objective: To evaluate the efficacy of SJW in relief of IBS after 12 weeks.

Design/Participants: This prospective, randomized, double-blinded, placebo-controlled trial included 70 volunteers (age range, 18 to 70 years) with previously diagnosed IBS recruited from Mayo Clinic. Participants had symptomatic IBS confirmed by Rome II criteria. Exclusion criteria included concurrent gastrointestinal disease, current severe depression (Center for Epidemiological Studies Depression Scale [CES-D] score ≥26), current or past psychotic disorder, significant concurrent medical disease, use of select mood, pain, or symptom-altering medications, alcohol/substance abuse, or use of IBS-specific drugs in the past 30 days.

Methods: Participants were randomized to SJW 450 mg orally twice daily or placebo for 12 weeks. Randomization was balanced based on gender and IBS subtype (ie, constipation-predominant, diarrhea-predominant, or mixed). The primary end point was self-reported overall IBS symptoms at 12 weeks measured by the validated bowel symptom score (BSS), a 100-mm visual analog scale. BSS was also used to measure severity of specific IBS symptoms including pain/discomfort, bloating, constipation, and diarrhea. IBS quality of life was measured by the IBS-QoL tool. Adequate relief (AR) of IBS symptoms was determined by yes/no answer to the question "Did you have adequate relief of your IBS symptoms over the last two weeks?" BSS, AR, and CES-D were assessed before medication initiation and every 2 weeks during the trial. IBS-QoL was evaluated at the beginning and end of the treatment period.

Results: 86% of participants were women (average age, 42 years). At 12 weeks, the placebo group had significantly lower (better) BSS than the SJW group. The placebo group also had significantly lower BSS for diarrhea, but not for other symptoms. Significantly more persons on placebo had AR from their IBS in ≥50% of the last 4 weeks of therapy. There were no serious side effects in either group.

Conclusions: SJW is less effective for the treatment of IBS than placebo.

Reviewer’s Comments: This small, well-done trial shows no benefit for SJW in IBS patients with mild-to-moderate or no depression. In patients who seek treatment for IBS and want to avoid prescription medications, reasonable options may include fiber, peppermint oil, or probiotics. SJW, however, does not appear to be an option. The American College of Gastroenterology Task Force on IBS has outlined some nonpharmacologic and some complementary and alternative treatment options for IBS in their position statement published January 2009 in the American Journal of Gastroenterology. (Reviewer-Melissa Hagman, MD).

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Keywords: Irritable Bowel Syndrome, St. John's Wort

Print Tag: Refer to original journal article
Sequential Therapy for *H. pylori* May be Superior to Usual Triple Therapy

*Sequential Therapy or Triple Therapy for Helicobacter pylori Infection: Systematic Review and Meta-Analysis of Randomized Controlled Trials in Adults and Children.*

Gatta L, Vakil N, et al:

Am J Gastroenterol 2009; 104 (December): 3069-3079

Sequential therapy appears to be more effective than triple therapy in the eradication of *H. pylori*, but further study is needed.

**Background:** First-line treatment for eradication of *Helicobacter pylori* is triple therapy (TT) with a proton pump inhibitor (PPI), amoxicillin 1g, and either clarithromycin 500 mg or metronidazole 500 mg, all twice daily for 7 to 10 days. This regimen previously led to *H. pylori* eradication rates of >90%. More recent rates have fallen to nearly 70%. Sequential therapy (ST) has shown promise for *H. pylori* eradication and includes a PPI and amoxicillin 1 g, both twice daily for 5 days followed by a PPI, clarithromycin 500 mg, and metronidazole 500 mg (or tinidazole), all twice daily, for 5 more days.

**Objective:** To determine the efficacy of ST compared to TT in *H. pylori* eradication.

**Methods:** This meta-analysis covers data through October 2008. Study inclusion criteria were: randomized controlled trial or controlled clinical trial with parallel group design comparing ST to TT; trial participants not previously treated for *H. pylori*; tests for eradication of *H. pylori* performed ≥4 weeks after treatment completion; and analysis by intention-to-treat.

**Results:** 13 studies were identified, with 3271 overall participants, including 3 studies assessing a total of 260 children (age, <18 years). Only 1 study was of good quality (Jadad score of 5), with most studies having Jadad scores of 3. In adults, *H. pylori* eradication rates were 91% for ST and 75.7% for TT (OR, 2.99; number needed-to-treat, 6). The superiority of ST over TT persisted regardless of the duration of TT (either 7 or 10 days), the underlying disease (peptic ulcer disease vs nonulcer dyspepsia), or the presence or absence of clarithromycin-resistant *H. pylori*. ST was also more effective than TT in children.

**Conclusions:** ST is superior to TT in the eradication of *H. pylori* with the caveats that some of the studies in this meta-analysis are of poor quality and most were performed in a single country (Italy). In the 2 reviewed studies based in Asia, ST was not superior to TT. The authors call for further studies before ST can be considered first-line therapy for *H. pylori* eradication.

**Reviewer’s Comments:** I will continue to follow current American College of Gastroenterology guidelines and use TT as first-line treatment for *H. pylori*. If clarithromycin resistance in my community grows to >20%, then I will substitute metronidazole for clarithromycin in the TT cocktail or I will use quadruple therapy (QT) with a PPI, bismuth, tetracycline, and metronidazole instead. In a January 2010 *American Journal of Gastroenterology* meta-analysis by Luther and colleagues, QT is as efficacious as TT. In patients who fail first attempts at eradication with TT, I will consider QT, levofloxacin-based therapy (PPI, levofloxacin, and amoxicillin), or perhaps ST. (Reviewer-Melissa Hagman, MD).

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**Keywords:** *Helicobacter pylori*, Peptic Ulcer Disease, Non-Ulcer Dyspepsia

**Print Tag:** Refer to original journal article
IBD Flare a Big Risk for Thromboembolism

Venous Thromboembolism During Active Disease and Remission in Inflammatory Bowel Disease: A Cohort Study.

Grainge MJ, West J, Card TR:

Lancet 2010; epub ahead of print (February 9):

Patients with IBD have increased risk for DVT/pulmonary embolism that goes up dramatically during a flare.

**Background:** Chronic medical illness is a well-known risk factor for venous thromboembolic disease (VTE), but risks associated with specific illnesses are vaguer.

**Objective:** To quantify the increased risk of VTE associated with inflammatory bowel disease (IBD).

**Design:** Retrospective case-control study.

**Participants/Methods:** 13,756 patients with IBD were matched to 71,672 controls and followed for 4 years on average.

**Results:** The absolute risk of VTE in the ambulatory control population was 0.4/1000 person-years. The risk for patients with IBD in remission was 0.9/1000 person-years: higher but still relatively low. However, for patients whose IBD was flaring, the risk was 6.4/1000 person-years, which is much higher and >7 times their baseline risk. Patients in a period of intermittent activity after a flare had a risk of 4.0/1000 person-years, in between the two. Compared to the ambulatory population, all inpatients had an increased risk of VTE. The control group without IBD had an absolute risk of 13.9/1000 person-years. Patients with IBD in remission had an absolute risk of 20.9, those with an active flare had an absolute risk of 37.5, and those with intermittent activity had an absolute risk of 29.3.

**Reviewer's Comments:** This is a statistically complex article, with lots of opportunity to get lost in the numbers. The key question is how it should change practice. When should patients with IBD be anticoagulated? Are they at excess risk of gastrointestinal bleeding when they have active disease? Thankfully, some of these questions have been answered, at least in part. There have been studies of bleeding risk in patients with IBD flares, and it appears that the use of anticoagulants is as safe as in any other patient. Deep venous thrombosis (DVT) prophylaxis for patients hospitalized with IBD flare is already recommended, especially for nonambulatory patients. The key area of ambiguity is what to do with patients who have IBD flares but do not require hospitalization. If you crunch some numbers, you figure out that they would have to treat around 1000 patients with anticoagulation for a 4-month-long IBD flare in order to prevent 1 DVT. This seems like a lot, particularly given how labor-intensive chronic anticoagulation can be. The author of an accompanying editorial argues that this merits a primary study of anticoagulation in this setting before changing practice, and I agree, unless a patient has other risk factors, such as a prior VTE event. However, one thing that is indisputable is that both our awareness of VTE and our efforts at encouraging nonpharmacologic prevention of DVT should be heightened in patients experiencing an IBD flare. (Reviewer-Christopher L. Knight, MD).

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Keywords: Inflammatory Bowel Disease, Thrombosis, Embolism

Print Tag: Refer to original journal article
10-Year Follow-Up of the Euro-Lupus Nephritis Trial

The 10-Year Follow-Up Data of the Euro-Lupus Nephritis Trial Comparing Low-Dose and High-Dose Intravenous Cyclophosphamide.

Houssiau FA, Vasconcelos C, et al:

Ann Rheum Dis 2010; 69 (January): 61-64

Long-term follow-up (10 years) of the landmark Euro-Lupus Nephritis Trial shows that a low-dose cyclophosphamide induction regimen results in comparable outcomes compared to higher dose regimens.

**Background:** Patients with lupus nephritis are commonly treated with induction therapy with cyclophosphamide (CY) or mycophenolate mofetil, in combination with prednisone. The Euro-Lupus Nephritis Trial (ELNT), first published in 2002, showed that lower doses of CY given for shorter induction periods were equivalent to higher dose induction regimens. It is necessary to follow patients with lupus nephritis for longer periods of time to capture important end points, such as progression of renal insufficiency or development of end-stage renal disease (ESRD).

**Objective:** This publication provides longer term follow-up for the ELNT study population.

**Participants/Methods:** 90 adult patients with moderately severe proliferative lupus nephritis and ≥500 mg of proteinuria per 24 hours were randomized to a standard tapering glucocorticoid regimen plus high-dose (HD) or low-dose (LD) intravenous cyclophosphamide (IVCY). HD IVCY consisted of 6 monthly pulses of 0.5 gm/m2 followed by 2 quarterly pulses. CY doses were increased to a maximum of 1500 mg per pulse if tolerated by measuring the day 14 white blood cell count nadir. The LD regimen consisted of 6 pulses of 500 mg of IVCY given every 2 weeks. In both groups, azathioprine was given as maintenance therapy after induction was completed. The principal end points were doubling of baseline serum creatinine (Cr), development of ESRD, or death.

**Results:** Only 6 patients were lost to follow-up over an average of 10 years of follow-up (3 in each group). There was no statistically significant difference in the risk of developing doubling of serum Cr, ESRD, or death between the 2 groups. There was no difference in the serum Cr and 24-hour proteinuria between the 2 groups. Patients in the LD IVCY group received a significantly lower cumulative dose of CY than the HD group (5.5 gm vs 9.5 gm, respectively; \( P <0.001 \)). Unexpectedly, more cancers were found in the LD group at an average follow-up of 100 months, although this difference did not reach statistical significance.

**Conclusions:** Patients with moderately severe lupus nephritis treated with low-dose IVCY enjoyed similar results compared to patients treated with traditional higher-dose regimens.

**Reviewer's Comments:** The "Euro-Lupus" low-dose IVCY regimen has become one of the accepted standard induction regimens for lupus nephritis (mycophenolate induction is an alternative). The important result of this study is that major outcomes did not differ between LD and HD regimens. Exposure to lower doses of CY might be associated with lower risks of side effects, including infection, impaired fertility, and secondary malignancies. The finding that more cancers were diagnosed in the low-dose group was unexpected and will need to be followed with ongoing clinical experience. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, Cyclophosphamide

Print Tag: Refer to original journal article
Both mycophenolate and cyclophosphamide are effective at reducing nonrenal manifestations of SLE.

**Background:** Patients with moderate or severe lupus nephritis are generally treated with immunosuppression consisting of induction therapy with IV cyclophosphamide (CYC or Cytoxan) or oral mycophenolate mofetil (MMF or CellCept) combined with glucocorticoids. Both are effective at reducing progression of renal disease, but the effect, if any, of induction therapy on common nonrenal effects of systemic lupus erythematosus (SLE) are not known.

**Objective:** To evaluate the effect of CYC or MMF on nonrenal disease in patients with lupus nephritis.

**Methods:** This was a substudy of the Apreva Lupus Management Study (ALMS) Group, a pharmaceutical company sponsored trial comparing induction with MMF to a standard CYC regimen. A total of 370 patients with SLE and moderately severe lupus nephritis were enrolled and randomized to open-label MMF versus IV CYC. Both groups received oral prednisone that was gradually tapered. While the primary purpose of this study was to examine renal end points, this substudy measured changes in nonrenal outcomes using a standard index called the British Isles Lupus Assessment Group (BILAG) disease activity index. Investigators were trained in this index before the study. They also measured complement levels and anti–double-stranded DNA antibody titers. Follow-up was 24 weeks.

**Results:** An equal number of patients were randomized to each arm; they were similar in baseline characteristics, including BILAG and Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) indices, and immunologic parameters. At the end of the study (24 weeks), 82.7% of patients remained (35 withdrew from the MMF group and 29 from the CYC group). Although patients were selected on the basis of lupus nephritis, >50% of patients had moderate or severe mucocutaneous or hematologic disease activity at study entry and >25% had moderate or severe musculoskeletal disease activity. Full clinical remission was achieved in approximately 60% of patients with moderate or severe disease activity in each organ system reviewed; results were comparable with MMF and CYC. Flares in SLE disease activity were rare in the study and comparable between the MMF and CYC groups. Immunologic responses as assessed by changes in complement and anti–double-stranded DNA titers were similar in both groups.

**Conclusions:** Treatment with either oral MMF or IV CYC resulted in substantial improvement in nonrenal and immunologic parameters of SLE.

**Reviewer’s Comments:** This is an important study that compares a new induction regimen consisting of MMF (CellCept) to an older, established regimen that uses IV CYC (Cytoxan). It will be important to establish whether MMF is a safe and effective alternative to the alkylating agent cyclophosphamide. While the follow-up in this study was short, the study found that induction with either MMF or CYC resulted in improvement in nonrenal measures of SLE in patients with lupus nephritis. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, Induction Therapy

Print Tag: Refer to original journal article
Melatonin should be given at bedtime following eastward travel to move the time of sleep earlier. After westward travel, a low dose should be taken if the traveler wakes up in the second half of the night to promote sleeping in.

**Background:** Jet lag is a benign problem, but daytime sleepiness, nighttime insomnia, and grumpiness can certainly make the first few days of a vacation or business trip less fun. **Objective:** To outline strategies for managing jet lag. **Results:** The author suggests 3 treatment strategies, which may be combined. First, the circadian rhythm may be reset by strategic light exposure, melatonin or both. For eastward travel, bright daylight first thing in the morning will shift the body clock to the new, earlier wake up time. Melatonin 0.5 to 3 mg should be taken at the new bedtime. For westward travel, bright light in the evening will move the endogenous bedtime later. A lower and shorter acting dose of melatonin, 0.5 mg, should be taken if awake in the second half of the night to help the traveler sleep later. Second, the timing and duration of sleep should be optimized. Before leaving, shift the sleep schedule 1 to 2 hours toward the destination time zone to shorten jet lag. Daytime naps should be kept short to avoid messing up nighttime sleep. Third, hypnotics such as zolpidem can help travelers get to sleep for the first 3 to 4 nights after arrival when travelling east. The author suggests caution in using hypnotics during a flight, as the traveler may wake up at their destination quite groggy and confused. Not surprisingly, caffeine is suggested to promote alertness during the day, but not too close to bedtime. Crossing more than 8 to 10 time zones is even more challenging for the circadian clock to adapt to. In this case, for the first 2 days, bright daylight should also be avoided at times it might inhibit adaptation: for several hours before dusk if travelling west and several hours after dawn if travelling east. Since it is easier to move the body’s clock backward than forward, some experts suggest treating all flights across more than 8 to 10 time zones as westward travel. **Conclusions:** Travelers (and physicians) crossing several time zones have several strategies that can minimize jet lag. **Reviewer’s Comments:** This is a sensible, easy to read summary with a table that clearly outlines recommendations in terms non-physician travelers can probably understand. Apart from the author’s suggestion, “Do not leave packing and other travel preparations to the last minute,” I will follow them for my next long trip. (Reviewer-Karen A. McDonough, MD).

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**Keywords:** Jet Lag, Travel Medicine, Melatonin, Circadian Rhythm

**Print Tag:** Refer to original journal article
Early Morphine Administration May Lessen Risk of PTSD

Morphine Use After Combat Injury in Iraq and Post-Traumatic Stress Disorder.

Holbrook TL, Galarneau MR, et al:


Early morphine use was associated with lower rates of PTSD in combat trauma victims in Iraq.

Background: Long-term, post-traumatic stress disorder (PTSD) can have a greater impact on quality of life than physical injuries sustained in military or civilian trauma.

Objective: To observe the effect of early morphine administration on the subsequent development of PTSD.

Design: Observational cohort study.

Participants: 696 U.S. military personnel injured in combat in Iraq.

Methods: Forward treatment facilities perform initial resuscitation, damage control surgery, and stabilize injured military personnel before they are transferred to higher level facilities. Each patient at a forward treatment facility has a standard data set collected, including the mechanism of injury, all treatment given, and a standardized assessment of the extent and severity of injuries. Investigators from the Naval Health Research Center reviewed the records of 790 consecutive patients treated at Navy facilities in Iraq, 2004 to 2006. Ninety-four were excluded because of severe brain injury. The subsequent development of PTSD was ascertained from military electronic medical records.

Results: Overall, 34% of these combat trauma patients developed PTSD. Of those who did, 61% received morphine during early resuscitation and trauma care compared with 76% of those who did not develop PTSD. There were no major differences in mechanism or severity of injury, presence or absence of mild traumatic brain injury, or amputation in those with and without a subsequent diagnosis of PTSD. Treatment with morphine during early resuscitation and stabilization was associated with a significantly lower risk of PTSD (odds ratio, 0.47). Other psychotropic medications were not commonly given. Nine percent received benzodiazepines early in trauma care, which appeared to have no effect on development of PTSD.

Conclusions: Early treatment with morphine after combat injury is associated with a lower risk of developing PTSD.

Reviewer's Comments: The authors discuss 2 potential mechanisms, early pain relief and interference with memory consolidation. Previous studies have shown an association between higher patient-reported pain levels in the acute period and subsequent PTSD. Few of us will care for combat trauma patients, but civilian trauma and severe medical illness, such as acute respiratory disease syndrome, can also lead to PTSD. Attention to pain control early may lessen the risk of PTSD after recovery. (Reviewer-Karen A. McDonough, MD).

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Keywords: Post-Traumatic Stress Disorder, Combat Injury, Pain Management

Print Tag: Refer to original journal article
Varenicline Appears Safe in Smokers With Stable CVD

Efficacy and Safety of Varenicline for Smoking Cessation in Patients With Cardiovascular Disease: A Randomized Trial.

Rigotti NA, Pipe AL, et al:

Circulation 2010; 121 (January 19): 221-229

Varenicline is effective and safe for smoking cessation in persons with stable cardiovascular disease.

**Background:** Varenicline (Chantix®) is an α4β2 nicotinic acetylcholine receptor partial agonist that improves smoking cessation rates in "healthy" smokers. Even though varenicline acts on a different receptor than nicotine, the safety of varenicline in smokers with cardiovascular disease (CVD) has been a concern.

**Objective:** To determine the efficacy and safety of varenicline in smokers with stable CVD.

**Design/Participants:** This multicenter, prospective, randomized, double-blind, placebo-controlled trial included 714 smokers (age range, 35 to 75 years) with stable CVD. Participants had to have smoked ≥10 cigarettes/day for the past year, want to quit smoking, and have a history of stable coronary artery disease, peripheral arterial disease, or cerebrovascular disease. Significant exclusion criteria included severe congestive heart failure, chronic obstructive pulmonary disease, renal insufficiency, or liver disease, depression or other psychiatric disorders, drug/alcohol abuse, uncontrolled diabetes mellitus or hypertension, any cardiovascular event, instability or procedure in the past 2 months, cancer, or smoking cessation medication use in past month.

**Methods:** Participants were randomized to varenicline (0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily) or placebo for 12 weeks, with a total follow-up of 52 weeks. Target quit date was 8 days after drug initiation. Assessment of smoking status, medication compliance, and adverse events occurred at weekly clinic visits during the drug treatment period, at a phone call 3 days after the quit date, and at 7 clinic visits and 5 phone calls spaced over weeks 13 to 52. At each clinic visit, the participants in both groups had vital signs and exhaled carbon monoxide (CO) levels checked. They also received 10 minutes of smoking cessation counseling. All participants also received brief cessation counseling with each phone call.

**Results:** The primary end point was 4-week continuous abstinence rate (CAR) in weeks 9 to 12 of drug treatment. Continuous abstinence was defined as self-reported abstinence and CO level ≤10 ppm. Forty-seven percent of the varenicline group and 13.9% of the placebo group met this end point (OR, 6.11; NNT, 3). The varenicline group also had better CAR for weeks 9 to 52 (19.2% compared to 7.2% for placebo; OR, 3.14; NNT, 9). Varenicline led to significantly more nausea/vomiting, constipation, and sleep disturbances (eg, abnormal dreams) than placebo. There was no difference in vital signs, mortality rates, cardiovascular events, or psychiatric side effects between the 2 groups.

**Conclusions:** Varenicline is effective for smoking cessation in persons with stable CVD and does not cause increases in cardiovascular events or mortality.

**Reviewer's Comments:** Smokers with CVD can reduce their risk of all-cause mortality by one-third through smoking cessation. Now, both varenicline and bupropion SR (Tonstad et al, Eur Heart J; 2003) have some data supporting safety in this population, with varenicline outperforming bupropion SR in head-to-head trials in "healthy" smokers. Any pharmacologic treatment should be coupled with psychosocial interventions to maximize outcomes. (Reviewer-Melissa Hagman, MD).

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Keywords: Smoking Cessation, Varenicline, Cardiovascular Disease

Print Tag: Refer to original journal article