Effective methods for decreasing pressure ulcer formation in older adults who spend a significant amount of time in a wheelchair include better nutrition, skin protection, and increasing patient mobility.

**Background:** Pressure ulcers are often preventable. Among the most vulnerable patients are those in wheelchairs and living in a nursing home. Because of the negative impact of pressure ulcers, many interventions have been tried in an effort to reduce the incidence of pressure ulcers.

**Design:** Randomized, prospective cohort study.

**Participants:** Participants were all nursing home residents ≥65 years of age who were in a wheelchair at least 6 hours a day. They all had a Braden score ≤18 along with a total activity and mobility score of ≤5. They were able to fit into the wheelchairs provided and were not yet using a wheelchair cushion.

**Methods:** Everyone received a fitted wheelchair. Patients were divided into 2 groups. The first group received segmented foam and a cushion to use in their wheelchair, and the other group received only segmented foam. Each patient was inspected for pressure ulcers to ensure there were none at baseline. Then, each person was checked weekly for pressure ulcer formation.

**Results:** Of the initial 232 participants, 180 reached the end point of the study; 42 were lost to follow-up. The control group had 8 ulcers that developed, and the intervention group developed 1 ulcer.

**Conclusions:** By having fitted wheelchairs along with skin protective cushions, elderly nursing home residents were better protected from pressure ulcer formation caused by sitting.

**Reviewer's Comments:** This study demonstrates how an inexpensive intervention can help such a costly problem such as pressure ulcers. I was particularly impressed with how they were able to strictly test the effectiveness of the cushion by instituting uniformity in wheelchairs. These cushions may show even more benefit in other settings because this cohort had a low incidence of pressure ulcers overall due to the fitted wheelchairs that were provided. Not everyone has that luxury. We all should consider wheelchair cushions for our patients when appropriate. (Reviewer-Ellyn M. Lee, MD).

**Keywords:** Pressure Ulcers, Prevention, Wheelchair Seat Cushions

Print Tag: Refer to original journal article
Compared with nonselective antiinflammatory drugs and selective cyclooxygenase-2 inhibitors, opioids are associated with more cardiovascular events, fractures, events leading to hospitalization, and all-cause mortality.

**Background:** Although analgesic prescriptions are extremely common (20% of all U.S. adults received one in 2006), there are few studies comparing the relative safety of different analgesic classes.

**Objective:** To compare the safety of nonselective antiinflammatory drugs (nsNSAIDs), selective cyclooxygenase-2 inhibitors (coxibs), and opioids, the 3 most frequently prescribed analgesics.

**Design:** Observational, comparative, propensity-matched, cohort study.

**Participants:** Medicare recipients from Pennsylvania and New Jersey receiving state-sponsored unrestricted medication benefits during the study period of 1999 through 2005 were included; all had a documented diagnosis of either osteoarthritis or rheumatoid arthritis. Patients on hospice or with a diagnosis of cancer in the last year were excluded, as were individuals who had received an nsNSAID, coxib, or opioid prescription within 180 days of beginning the study.

**Methods:** The authors chose a propensity-matched cohort design because a randomized controlled trial is impractical for studying adverse analgesic effects. Thirty-nine different variables, including demographic factors, comorbidity and nonanalgesic medications used, were combined to create a propensity score, which facilitated close matching of cohorts whose members were similar in all respects except for the specific analgesic class each was prescribed. A cohort was created for each of the 3 most commonly prescribed analgesic classes (nsNSAIDs, coxibs, and opioids). Each cohort was then monitored for 15 individual adverse effects that were also aggregated into the 3 composite categories of cardiovascular, upper/lower gastrointestinal (GI) bleeding; and fracture. Severe safety events, namely any event leading to hospitalization, any event leading to acute hospitalization and subsequent death, and deaths (all-cause mortality) were also measured.

**Results:** 12,840 out of a potential 163,714 individuals were successfully matched to 1 of the 3 cohorts. Coxibs and opioids were associated with more cardiovascular events than nsNSAIDs. Opioids and nsNSAIDs had similar risks for GI bleeding, both of which were greater than the risk for coxibs. Opioids had a much greater (almost 4.5 times greater) fracture risk than coxibs and nsNSAIDs. Opioids had a greater risk of safety events leading to hospitalization and a greater risk of all-cause mortality than nsNSAIDs and coxibs. When rofecoxib and valdecoxib (2 coxibs that were taken off the market since the beginning of this study) were removed from the mix, cardiovascular risk for coxibs (now limited to celecoxib only) was no longer greater than that for nsNSAIDs.

**Conclusions:** Although adverse effects of analgesics differ somewhat by class, opioids have an overall greater safety risk than nsNSAIDs and coxibs.

**Reviewer's Comments:** A notable limitation of this study is that the authors were not able to factor in possible use of over-the-counter NSAIDs. The strong association that the authors found between opioids and serious long-term adverse safety outcomes, however, is invaluable new information which will hopefully inspire additional research and make prescribers even more thoughtful about their approach to treating pain in older adults. (Reviewer-Carol L. Howe, MD, MLS).

**Keywords:** Arthritis, Analgesics, Safety, Nonselective NSAIDs, Opioids

**Print Tag:** Refer to original journal article
Statins Show Significant Promise in Patients With NAFLD

Safety and Efficacy of Long-Term Statin Treatment for Cardiovascular Events in Patients With Coronary Heart Disease and Abnormal Liver Tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: A Post-Hoc Analysis.

Athyros VG, Tziomalos K, et al:

Lancet 2010; 376 (December 4): 1916-1922

In patients with abnormal liver function tests likely secondary to nonalcoholic fatty liver disease, statins decrease mortality and improve liver function.

**Background:** Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver tests in the developed world, and its presence confers higher all-cause mortality, which is mainly due to cardiovascular disease (CVD). Although statins are part of the therapeutic strategy for NAFLD, the risk-to-benefit ratio of statin use in these patients has not been investigated in outcome studies.

**Objective:** To analyze the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study to determine the risk-to-benefit ratio of treatment with statins in patients with NAFLD.

**Methods:** The GREACE study was a prospective randomized trial of 1600 patients with coronary artery disease <75 years of age who had LDL levels >2.6 mmol/L (approximately 101 mg/dL) and triglycerides <4.5 mmol/L (approximately 399 mg/dL). One group was randomized to statin use, while the usual care group was treated according to the treating physician's standard of care, which could include statins. This post-hoc analysis of the GREACE study examined the primary outcome of risk reduction for first recurrent cardiovascular event in the form of all-cause mortality, coronary heart disease (CHD) morbidity and mortality, or stroke in patients with mildly to moderately abnormal liver tests receiving a statin compared to those not treated with statin.

**Results:** Patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal were not included in the study. Mild to moderate increases in serum concentrations of AST or ALT were noted in 437 of 1600 patients at baseline. Among the patients who had abnormal liver function tests, 22 (9.7%) of the 227 cases taking a statin had a cardiovascular event, which was a 68% risk reduction over 63 patients with a cardiovascular event of the 210 (30.0%) not taking a statin (P <0.0001). This benefit was greater than that reported for statin use in this study in those with normal liver tests. Among patients who had abnormal liver tests, those who received statins had a reduction in liver tests, while those who did not receive statins had a further rise in liver tests during follow-up.

**Conclusions:** This study showed the significant reduction of cardiovascular events as well as improvement in liver function with statin use in patients with abnormal liver function tests potentially attributable to NAFLD, as those with alcohol misuse and other liver diseases were excluded. NAFLD has significant overlap with diabetes and metabolic syndrome and has been thought of as insulin resistance manifested in the liver. In these patients who are at a higher risk for mortality that is mainly secondary to cardiovascular disease, statins appear to be a promising treatment. Statin use decreases mortality and improves liver function tests in patients with elevated liver function tests attributable to fatty liver disease.

**Reviewer's Comments:** This post-hoc analysis shows significant promise with statins for those with mildly to moderately abnormal liver tests potentially attributable to NAFLD. These patients represent a high-risk group and should be identified as such; with this identification aggressive treatment may be warranted. (Reviewer-Stephen Olex, MD).

Keywords: CHD, Cardiovascular Events, Abnormal Liver Tests, Statins, NAFLD

Print Tag: Refer to original journal article
Perhaps Patients Do Not Need to Stop Low-Dose ASA Before iFOBT

Low-Dose Aspirin Use and Performance of Immunochemical Fecal Occult Blood Tests.

Brenner H, Tao S, Haug U:

JAMA 2010; 304 (December 8): 2513-2520

Low-dose aspirin use increases the sensitivity of some immunochemical fecal occult blood tests.

**Background:** Should patients taking low-dose aspirin (ASA) for chemoprophylaxis against vascular events stop the medication before performing fecal occult blood tests (FOBT)? Does low-dose ASA increase the false-positive rate of FOBT?

**Objective:** To assess the effect of low-dose ASA use on immunochemical FOBT (iFOBT) performance.

**Design:** Diagnostic study of iFOBT accuracy in patients scheduled to undergo screening colonoscopy.

**Methods:** Patients were enrolled between 2005 and 2009. Stool samples underwent testing with 2 different iFOBT assays, and then patients underwent colonoscopy. The mean age of the 1979 patients enrolled was 62 years; 233 were users of low-dose ASA and 1746 were nonusers. Sensitivity, specificity, and area under receiver operating characteristic (ROC) curves were determined for each iFOBT method in both low-dose ASA users and nonusers. An advanced colon neoplasm was defined as cancer or an advanced adenoma >1 cm or containing tubulovillous components or high-grade dysplasia.

**Results:** Advanced colon neoplasms were found in 10% of patients in both groups. Each of the iFOBT assays was significantly more sensitive in low-dose ASA users than in nonusers. Sensitivities in ASA users were 71% (95% CI, 49% to 87%) and 58% (37% to 78%) as compared with 36% (29% to 43%) and 32% (25% to 39%) in nonusers (P = 0.003 for both comparisons). Specificities were slightly lower among ASA users than nonusers (86% for each iFOBT assay in ASA users vs 89% and 91% in nonusers). The areas under the ROCs were 0.79 and 0.73 for users and 0.67 and 0.65 for nonusers (P = 0.05 and P = 0.17, respectively). (Area under ROC for an ideal screening test = 1 and for a worthless test = 0.5).

**Conclusions:** For 2 iFOBT assays, low-dose ASA use was associated with much higher sensitivity and slightly lower specificity for detecting advanced colorectal neoplasms.

**Reviewer’s Comments:** This study addresses a very practical management point. Based on these results, we do not need to instruct patients to stop taking low-dose aspirin prior to performing iFOBT testing. Rather than reducing sensitivity, the results suggest that low-dose ASA increases bleeding from colonic neoplasms more than from other sources. One caveat deserves mention. These results cannot be generalized to FOBT screening with guaiac cards. Because iFOBTs react specifically to globin, which is degraded enzymatically during its passage through the gastrointestinal tract, they are less likely to detect bleeding from the upper gastrointestinal tract than guaiac cards. (Reviewer-John V.L. Sheffield, MD).

Keywords: Colon Cancer Screening, Aspirin, Fecal Occult Blood Tests

Print Tag: Refer to original journal article
Prostate-specific antigen screening for prostate cancer continues to struggle against evidence suggesting it is not effective in increasing survival.

Objective: To determine the best method of screening for prostate cancer.

Design/Methods: A systematic review was performed to include all randomized, controlled trials (RCTs) comparing prostate cancer screening with prostate-specific antigen (PSA) to no screening. Compatible results were also compiled in a meta-analysis.

Results: 6 individual RCTs have been done to date with 387,286 total patients. Screening was associated with a greater chance of being diagnosed with prostate cancer (RR, 1.46), especially stage 1 (RR, 1.95). However, screening was not associated with improved cancer-specific survival (RR, 0.88; 95% CI, 0.71 to 1.09; \( P =0.25 \)) or overall survival (RR, 0.99; 95% CI, 0.97 to 1.01; \( P =0.44 \)).

Conclusions: The data from all RCTs of screening with PSA for prostate cancer reveals no survival benefit for screening. However, every study had at least one significant methodological flaw. In addition, information on quality of life effects, harms, and costs is lacking.

Reviewer’s Comments: Djulbegovic and colleagues reported the results of their systematic review and meta-analysis of prostate cancer screening trials using PSA. In addition to 4 recent studies from the United States and Europe, they found 2 previous RCTs from Quebec and Sweden, which were included. The methodological quality of each individual study was critically assessed. In addition, the quality of evidence for each specific outcome was evaluated, using an international grading system known as "GRADE." The authors were able to demonstrate that the current quality of evidence for overall survival, for example, is "moderate," while evidence for the effects of screening specifically on stage II prostate cancer (arguably the stage in which we hope to make the most impact on the natural history of the disease) is "very low." The meta-analysis revealed a 46% relative increase in the diagnosis of prostate cancer from screening; most of these cases were stage I disease. For higher stages, there was no change in diagnosis with screening, although the quality of evidence was low. Finally, based on moderate quality evidence, there was no change in cancer-specific or overall mortality with screening. In fact, the 95% confidence intervals for overall mortality were incredibly narrow (0.97 to 1.01), suggesting that it may be hard to dispute this finding with future studies. There are arguments against these findings. It may be inappropriate to combine these studies in a meta-analysis due to methodological flaws that make them incompatible; follow-up may need to be longer; high-risk populations may need exploration; and other important outcomes may need consideration, such as metastatic disease and quality of life. What appears to be clear is that we sorely need a better test. We can't revert back to pre-PSA era. Therefore, we should be vigilant against overtreatment of patients, at least until a better test becomes available. (Reviewer-Steven E. Canfield, MD).

Keywords: Prostate Cancer, Screening, PSA

Print Tag: Refer to original journal article
Can Trained Dogs Detect Prostate Cancer?

Olfactory Detection of Prostate Cancer by Dogs Sniffing Urine: A Step Forward in Early Diagnosis.

Eur Urol 2011; 59 (February): 197-201

Sensitivity and specificity are approximately 91% when a trained canine is utilized to detect prostate cancer.

**Background:** Volatile organic compounds in urine have been suggested as potential markers of cancer detection. Recently, a small study found that bladder cancer could be detected by a trained dog, so why not try a similar experiment with prostate cancer patients?

**Objective:** To evaluate the sensitivity and specificity of dogs trained to detect prostate cancer from urine samples of humans.

**Methods:** A Belgian Malinois shepherd dog was trained for >2 years to scent and locate urine of men with prostate cancer. After this time, a double-blind procedure was utilized. Urine was used from 66 patients referred to a urologist for an elevated prostate-specific antigen or abnormal digital rectal examination (DRE). All patients had a biopsy; 33 patients had cancer and 33 were negative biopsy controls. During each "run," there were 5 samples without cancer and 1 sample with cancer (6 total). The dog had 1 chance to signal which of the samples were from a patient with cancer.

**Results:** The dog detected the correct cancer sample in 30 of the 33 cases presented to it. Of 3 cases that the dog missed, 1 patient was rebiopsied and cancer was found. Sensitivity and specificity were both 91%.

**Conclusions:** Dogs can be trained to detect prostate cancer, but this study also suggests that specific compounds can be located in the urine and used as novel cancer detection agents.

**Reviewer's Comments:** Holy canine conundrum Batman! This is one small paw step for man and one giant leap for mankind. And I always thought that the only reason my dog buried himself in my clothing (notice the politically correct wording) when I came home from work was because he was looking for a doggy treat and not because he was looking for prostate cancer. Still, it is intriguing that dogs have been trained to detect explosives, drugs, and squirrels, so why not other compounds that can detect cancer or other diseases? There have been some preliminary studies already completed in individuals with bladder, breast, and lung cancer that have demonstrated the ability of some dogs to detect these tumors with a greater chance than just basic probability or luck. The bigger issue may come down to dietary supplements (ahh and you thought this article had nothing to do with my area of interest) because a variety of pills can change urine color and smell. For example, certain B-vitamins such as vitamin B2 (riboflavin) can turn the urine a harmless fluorescent yellow color. Other herbal supplements and foods could change the smell of the urine. For example, I would love to see what a dog can do after someone eats a pound of asparagus (ouch!). The bigger point again my friends is that perhaps dogs should be used to find compounds that could eventually be tested as screening markers since humans could always use some help in this area. (Reviewer-Mark A. Moyad, MD, MPH).

**Keywords:** Prostate Cancer Detection, Olfactory Detection, Urine, Dogs

**Print Tag:** Refer to original journal article
Behavioral therapies are a key component to achieving urine continence in patients who are incontinent after prostatectomy.

**Background:** The use of behavioral therapies, biofeedback, and electrical stimulation of pelvic muscles has been shown to be useful in treating urine incontinence in the immediate postoperative period after prostatectomy in past studies. These methods of intervention in the setting of urine incontinence that persist past 1 year in postprostatectomy patients have not been previously analyzed.

**Objective:** To further assess the effectiveness of nonsurgical and non-medication interventions in the setting of postprostatectomy urine incontinence.

**Design:** Prospective, randomized, controlled trial.

**Participants:** 208 men participated in this study. They all suffered from postprostatectomy urine incontinence at least 1 year after surgery. Approximately 25% were African American, and 75% were white.

**Methods:** Outcomes were measured in the percent reduction of episodes of urine incontinence at 8 weeks as recorded in the weekly bladder diary. Questionnaires were also used to assess quality of life and measure possible changes in quality of life after 8 weeks of treatment. Patients were then seen at 6 months and 12 months.

**Interventions:** Participants were broken up into 3 groups: those who received only behavioral therapy; those who received behavioral therapy plus biofeedback and home electrical stimulation of pelvic muscles; and a delayed treatment group that served as a control group. Behavioral therapy included pelvic floor muscle contraction instruction, fluid management, and bladder diaries recording voiding, accidents, and the number of pelvic floor muscle exercises done. These diaries were reviewed and further instruction was given on bladder control strategies. Patients randomized to behavioral therapy plus biofeedback and electrical stimulation received similar teaching but with the addition of biofeedback during sessions of teaching on pelvic floor muscles and a home electrical stimulation unit and instruction and directions for its use. The control group just kept bladder diaries without any instruction.

**Results:** At 8 weeks, the behavioral therapy group had a mean reduction of 55% of incontinence episodes as compared to the control group. Those who received behavior therapy plus biofeedback and electrical stimulation had a 51% mean reduction of incontinence episodes. These improvements were sustained after 12 months. Ninety percent of the participants in the treatment groups described their symptoms as "better" or "much better" as compared to controls.

**Conclusions:** Behavioral therapies for postprostatectomy urine incontinence are a key part of a treatment plan for a patient. The addition of electrical stimulation and biofeedback did not improve upon the results achieved by behavioral therapy.

**Reviewer's Comments:** This is an important article that directs our treatment plans for men who have had urine incontinence after prostate removal. (Reviewer-Sara Rahman, MD).

**Keywords:** Incontinence, Behavioral Therapy, Biofeedback, Pelvic Floor Electrical Stimulation

**Print Tag:** Refer to original journal article
In children with uncomplicated otitis media and normal risk, only 12 in 100 benefit from antibiotics, and most antibiotics are equivalent in clinical success.

**Objective:** To look at the precision and accuracy of acute otitis media diagnosis, to assess the effect of the pneumococcal vaccine in microbial epidemiology, to review the evidence about the decision to treat with antibiotics, and to examine the effectiveness and adverse events of various antibiotics.

**Design/Methods:** Systematic review of articles from 1999 to 2010 on otitis media, which is the most common reason for which antibiotics are prescribed for US children, although there is wide variation in diagnosis and treatment.

**Results:** Regarding diagnosis, the authors concede that the accuracy of clinical features is clouded by the lack of a consistent gold standard, such as tympanocentesis. Of parent-reported symptoms, ear pain and ear rubbing are only modestly associated with otitis media. Of otoscopic findings, a bulging eardrum was most closely associated with the diagnosis. Immobility on pneumatic otoscopy was also strongly associated with infection, but redness had a much lower correlation with the likelihood of acute otitis media. Since the pneumococcal vaccine, most studies have found that *Haemophilus influenzae* has become more prevalent as a middle ear isolate with *Streptococcus pneumoniae* less prevalent, although it has remained important, particularly the non-vaccine serotypes. The authors examined many studies that looked at the benefits of antibiotic treatment, the use of amoxicillin versus placebo, immediate versus delayed antibiotics, short- and long-term antibiotic harms, and comparative antibiotic effectiveness. Of 100 average-risk children with otitis media, 80% will get better within 3 days without antibiotics. Amoxicillin does improve the outcome. The authors estimated that if all 100 were treated with amoxicillin, an additional 12 would improve, but 3 to 10 would develop rash and 5 to 10 would develop diarrhea. It is these risks versus benefits, including long-term issues related to antibiotic resistance, that clinicians must weigh before deciding on therapy. When the authors looked at uncomplicated otitis cases in normal-risk children, they could find no evidence of the superiority of amoxicillin over any other antibiotic, including cefdinir, cefixime, and ceftriaxone.

**Conclusions:** Otoscopic findings remain critical to accurate acute otitis media diagnosis. Since the introduction of the pneumococcal vaccine, microbiology of inner ear pathology has changed. Compared to no treatment, antibiotics are modestly effective but may cause adverse events in 4% to 10%. Most antibiotics are equivalent in clinical success.

**Reviewer's Comments:** Otitis media is certainly a bread-and-butter issue for pediatricians and many factors, clinical and parental, go into the decision to treat or not to treat. This paper is a thorough summary for pediatricians to gauge their practice against the latest in evidence-based medicine. In the stay-tuned-for-future-attractions category, new American Academy of Pediatrics otitis media practice guidelines are currently in preparation. We'll all be ears. (Reviewer-Mark F. Ditmar, MD).

Keywords: Otitis Media

Print Tag: Refer to original journal article
Confusion Exists About Management of HPV Testing Results

Common Abnormal Results of Pap and Human Papillomavirus Cotesting. What Physicians Are Recommending for Management.

Berkowitz Z, Saraiya M, et al:

Obstet Gynecol 2010; 116 (December): 1332-1340

Mildly abnormal cytology results are often aggressively managed; HPV testing, when appropriately used, can reduce unnecessary interventions.

**Objective:** To study the adherence of physicians to practice guidelines for common abnormal results of pap and human papilloma virus (HPV) testing.

**Design:** Cross-sectional national representative survey.

**Participants:** 950 primary care physicians.

**Methods:** Physicians in family practice, general practice, obstetrics and gynecology, and internal medicine were invited to participate in a survey conducted between September 2006 and May 2007 to assess cervical cancer screening recommendations and management. A total of 1,212 physicians completed the survey for an overall response rate of 67.5%. Of these, 950 Pap test providers who recommended HPV testing are included in the study. Primary outcomes of the survey were based on 2 clinical scenarios describing a patient aged 35 years who (1) has a negative Pap test and a positive HPV test or (2) has a Pap test result of atypical squamous cells of undetermined significance and a negative HPV test. Investigators used a multivariable logistic regression analysis to determine physician adherence to current guideline recommendations. They also collected data on physician demographics, including practice characteristics, screening beliefs, sex, race, ethnicity, year of graduation from medical school, board certification, and medical school affiliations. The correct guideline approach in women with a discordant test (negative Pap smear but positive HPV test), is that follow-up should occur within 6 to 12 months with both Pap smear and HPV study. For those women who have a Pap test with a mildly abnormal finding and a negative HPV test, repeat Pap test should be ordered in 12 months with no additional HPV test.

**Results:** There was adherence to management guidelines by 54.3% of physicians in management of a discordant test when there was a negative Pap smear in a positive HPV test. Only 12.2% of physicians were guideline-adherent in recommendations for management of an abnormal cytology result with a negative HPV test. There was no significant difference among physicians’ specialties in management of discordant results, but there was significant variability in adherence to guidelines in mildly abnormal results with 19.8% of gynecologists adhering to guidelines as compared to 9.3% of general practitioners and 11% of internists.

**Conclusions:** Current management guidelines are not adhered to by many physicians even for the most common abnormal cytology results or HPV results.

**Reviewer’s Comments:** These authors believe that guidelines for management of abnormal cervical cytology should be simplified using evidence-based methodology. Some of their suggestions include updated educational materials, use of electronic medical records, reminder systems, and decision analysis programs. (Reviewer-John C. Jennings, MD).

Keywords: HPV Testing Recommendations, Adherence, Abnormal Results

Print Tag: Refer to original journal article
Delayed-Release Therapy Improves Nausea, Vomiting in Pregnancy

Effectiveness of Delayed-Release Doxylamine and Pyridoxine for Nausea and Vomiting of Pregnancy: A Randomized Placebo Controlled Trial.

Koren G, Clark S, et al:

Am J Obst Gynecol 2010; 203 (December): 571.e1-571.e7

The delayed-release combination of doxylamine succinate and pyridoxine hydrochloride is an effective treatment for nausea and vomiting of pregnancy.

Objective: To determine the efficacy of the combination of doxylamine succinate and pyridoxine hydrochloride (Diclectin) in the treatment of nausea and vomiting in pregnancy compared to using a placebo.

Design: Randomized, double-blind, multi-center placebo controlled study.

Participants: 259 pregnant patients with nausea and vomiting.

Methods: A delayed-release combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride was used for the treatment of nausea and vomiting of pregnancy. Patients received a minimum of 2 tablets per day to a maximum of 4 tablets per day depending on the severity and frequency of symptoms from the nausea and vomiting. Either a placebo or study medication was administered for 14 days. Use of additional medications for nausea and vomiting was assessed along with adverse events for each patient. A pregnancy-unique, quantification-of-emesis score was completed each morning prior to the medication being given. Patients also completed a global well-being assessment during the study. At the completion of the 2-week study, patients were offered use of the product that they had received. Primary outcome was change in pregnancy-unique, quantification-of-emesis score during the study. This score ranged from 3, which were the low symptoms, compared to 15, which were the most severe symptoms. Quality-of-life assessment ranged from 0 (worst) to 10 (best).

Results: 131 patients were in the study group using Diclectin and 128 patients were in the placebo group. There was a significant improvement in the symptoms associated with nausea and vomiting of pregnancy in the Diclectin group compared to the placebo group. Also, in the global assessment of overall well being, there was marked improvement in the group taking Diclectin versus those taking a placebo. At the end of the medication trial, 48.9% of patients taking Diclectin requested continued use of the medication compared to 32.8% of the placebo group. Also, approximately 36% of patients in the placebo group used other therapies for nausea and vomiting in pregnancy compared to 23.7% in the Diclectin group. There were no adverse outcomes in the study group compared to the placebo group.

Conclusions: A delayed-release combination of doxylamine succinate and pyridoxine hydrochloride is an effective therapy for treating nausea and vomiting of pregnancy.

Reviewer's Comments: It appears that the Diclectin formulation of doxylamine succinate and pyridoxine hydrochloride is effective in the treatment of symptoms of nausea and vomiting in pregnancy without increased risk of adverse events. The ability to significantly improve the symptoms of nausea and vomiting of pregnancy not only has ramifications with respect to patient care, but also has economic impact when considering loss of work with an 8- to 10-week duration of nausea and vomiting in pregnancy symptoms. (Reviewer-Thomas N. Tabb, MD).

Keywords: Nausea, Vomiting, Pregnancy, Diclectin

Print Tag: Refer to original journal article
In this meta-analysis, more intensive statin therapy resulted in greater reductions in major cardiovascular events than less intensive statin therapy. More intensive therapy also appeared to be safe.

**Background:** Trials that have specifically studied more intensive statin treatment have been suggestive of greater cardiovascular risk reduction compared with less intensive treatment, but several studies have had nonsignificant results.

**Objective:** To use individual specific data to evaluate the efficacy and safety of more intensive statin therapy.

**Design/Methods:** This meta-analysis included trials of statin therapy that lasted at least 2 years and had at least 1000 participants. The primary outcome was major cardiovascular events over an average follow-up of 5.1 years. Analysis was performed by intention to treat. The effect size was reported by change in outcome per 1.0 mmol/L reduction in LDL cholesterol (1.0 mmol/L cholesterol = 38.67 mg/dL).

**Results:** A total of 5 studies comparing more intensive statin therapy to less intensive statin therapy were included, 2 with acute coronary syndromes (8659 patients) and 3 with stable coronary disease (30,953 patients). At baseline, the average LDL cholesterol was 2.53 mmol/L (97.8 mg/dL); it was reduced an average of 0.51 mmol/L (19.72 mg/dL). Subjects in the intensive treatment arms experienced major cardiovascular events at a lower rate than subjects in the less intensive treatment arms. The reduction in major cardiovascular events was 28% per 1.0 mmol/L reduction in LDL cholesterol (95% CI, 22 to 34; \( P <0.0001 \)), similar to the reduction observed in a meta-analysis of statin versus placebo trials (21% per 1.0 mmol/L reduction in LDL cholesterol). Each of the constituent elements of the composite outcome was significantly reduced. There was a significant reduction in all strokes, but a nonsignificant increase in hemorrhagic strokes was associated with more intensive statin therapy. There was no increase in first cancers diagnosed among patients randomized to more intensive treatment. Rhabdomyolysis was rare, but there appeared to be an excess of rhabdomyolysis in patients treated with 80 mg of simvastatin compared to 20 mg.

**Conclusions:** More intensive statin treatment resulted in further reductions in cardiovascular risk than less intensive treatment.

**Reviewer's Comments:** This meta-analysis adds to our understanding of statin therapy, suggesting that more intensive therapy reduces cardiovascular risk more than less intensive therapy, to the tune of about a 20% relative reduction in risk for every 1.0 mmol/L (39 mg/dL) reduction in LDL cholesterol. More intensive therapy appeared safe, particularly when using more potent statins (atorvastatin or rosuvastatin) rather than higher doses of less potent statins. It remains essential to consider absolute cardiovascular risk when making clinical decisions about statin therapy, but this study supports the approach of more intensive lipid lowering in patients with the highest cardiovascular risk. (Reviewer-Paul R. Sutton, PhD, MD.)

Keywords: Statin Therapy, Intensive Statin Therapy, Meta-Analysis

Print Tag: Refer to original journal article
**Beta-Blockers Before Vascular Surgery -- The Earlier, the Better**


J Am Coll Cardiol 2010; 56 (November 30): 1922-1929

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**β-blockers initiated >1 week before vascular surgery are more cardioprotective than therapy that is initiated <1 week before surgery.**

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**Background:** β-blockers have been demonstrated to have benefit in preventing perioperative cardiovascular complications. Among the mechanisms thought to contribute to the cardioprotective effect are alterations in sympathetic nervous system function and a decrease in inflammatory markers such as C-reactive protein (CRP) that may result in plaque stabilization. Although multiple studies have shown benefit to perioperative β-blockade, the timing of initiation has not been well defined.

**Objective:** To evaluate the timing of perioperative β-blockade initiation in a cohort of patients undergoing vascular surgery.

**Participants/Methods:** 940 patients undergoing vascular surgery, either open or endovascular, were evaluated. Exclusion criteria were heart rate <50 bpm, prior randomization to β-blocker treatment, or emergency surgery. β-blocker initiation was begun either <1 week, >1 week to 4 weeks, or >4 weeks before surgery. For patients in whom β-blockers were started >1 week before surgery, a second clinic visit 1 week after initiation of therapy was utilized to titrate dosing to ensure a resting heart rate of 60 to 70 bpm. The usual cardiovascular comorbidities were assessed, and CRP levels were drawn 1 day before surgery. The primary outcome was cardiovascular events within 30 days (myocardial infarction or ischemia, stroke, or death), with secondary outcomes of perioperative heart rate and CRP levels. Mean follow-up was 2.2 years.

**Results:** 70% of patients received bisoprolol, 20% received metoprolol, 5% received atenolol, and 5% received other β-blockers; 77% of patients were men, and the mean age was 67 years. Those receiving β-blockers >1 to 4 weeks and >4 weeks before surgery had a lower resting heart rate on the day of surgery than those who began therapy <1 week before surgery (70 and 66 vs 74 bpm). There was no difference in CRP levels the day before surgery. Of patients in the <1 week group, 27% had perioperative cardiovascular events compared with 15% of those whose therapy was initiated >1 to 4 weeks and >4 weeks preoperatively (HR, 0.46 and 0.48, respectively). The majority of events were troponin release. The hazard ratios for long-term mortality for those with β-blocker initiated >1 to 4 weeks and >4 weeks compared to those with therapy begun at <1 week were 0.55 and 0.50, respectively.

**Conclusions:** Perioperative β-blockade is associated with improved cardiovascular outcomes when begun >1 week before surgery rather than <1 week before surgery. There is no difference in CRP levels, suggesting that the mechanism is not likely related to inflammation but may be related to heart rate control.

**Reviewer's Comments:** This study demonstrates that, among patients undergoing vascular surgery, there is greater cardioprotective benefit to beginning β-blockers well before surgery, likely related to heart rate control rather than inflammation. This would argue that appropriate initiation of β-blockers before surgery should happen more than a week before surgery, and the dose should be titrated to resting heart rate. (Reviewer-Karen Stout, MD).

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Keywords: Vascular Surgery, Perioperative β-Blockade

Print Tag: Refer to original journal article
Injecting steroids for tendonitis offers minimal short-term benefit, and at least at the elbow, may decrease long-term improvement.

**Background:** Despite the fact that steroids have been a part of medical care for >60 years, outcome-based evidence on their use for musculoskeletal problems is limited.

**Objective:** To assess the benefits of injections (including corticosteroids) for treatment of tendinopathy.

**Design:** Systematic review and meta-analysis.

**Methods:** 3824 trials were assessed, of which 41 met criteria; the 41 trials included 2672 participants. The majority of trials were of corticosteroid injections for either lateral epicondylitis or rotator cuff tendinitis. However, a minority of trials included other anatomic locations, and other injections, such as sodium hyaluronate, prolotherapy, platelet-rich plasma, and even botulinum toxin.

**Results:** In lateral epicondylitis, there is strong evidence for short-term benefit with steroid injections, but less pain reduction at 6 months compared with nonsteroidals, physiotherapy, platelet-rich plasma, and no intervention at all. In rotator cuff tendinitis, there was benefit when compared to placebo, but no short-term benefit was seen in studies comparing to nonsteroidal and minimal benefit compared to physical therapy. Out of 416 patients who received steroid injections in placebo controlled trials, there were 38 cases of atrophy, 31 cases of pain, 2 cases of depigmentation, and 1 case of tendon rupture of the Achilles tendon.

**Conclusions:** Corticosteroid injections are effective in the short term, and noncorticosteroid injects may be beneficial for long-term treatment of lateral epicondylalgia.

**Reviewer's Comments:** The findings for lateral epicondylitis are the most concerning, as there is evidence that by using steroid injections, we may be at least delaying and at worst diminishing prospects for overall recovery. The findings in rotator cuff tendinitis are also somewhat disappointing. There is also less evidence of long-term harm (although this is predominantly due to a lack of long-term data, and should not be confused with evidence that shows safety), so it is less clear how to direct patients with rotator cuff pain. In skilled hands, tendon rupture is a rare complication, but subcutaneous atrophy remains relatively common, occurring in almost 10% of procedures. For those of us who continue to give steroid injections, clearly atrophy and depigmentation should be mentioned as possible complications when obtaining informed consent. It is also worth reiterating that this review looked specifically at tendinopathies and not at intra-articular injections. (Reviewer-Christopher L. Knight, MD).

**Keywords:** Tendonitis, Injections, Corticosteroids, Efficacy, Safety

**Print Tag:** Refer to original journal article
High Levels of HDL Associated With Decreased Incidence of Dementia

Association of Higher Levels of High-Density Lipoprotein Cholesterol in Elderly Individuals and Lower Risk of Late-Onset Alzheimer Disease.

Reitz C, Tang M-X, et al:

Arch Neurol 2010; 67 (December): 1491-1497

High HDL levels are associated with a decreased incidence of dementia.

**Background:** Dyslipidemia is an established risk factor for both vascular disease and the dementia that results from vascular disease. However, there is also evidence that cholesterol prevents beta amyloid degradation and inflammation in the brain leading to Alzheimer disease and that low cholesterol induces brain injury associated with Alzheimer disease.

**Objective:** To determine the association between the lipid profile and the incidence of dementia.

**Design:** Prospective cohort trial.

**Participants:** Randomly selected Medicare recipients residing in Manhattan, New York.

**Methods:** Initially, 2190 participants were recruited; 1060 were eliminated due to a diagnosis of dementia at baseline, incomplete lipid data, or were lost to follow-up. Demographic information, body mass index (BMI), the presence of ApoE4, a diagnosis of diabetes, hypertension, or heart disease, defined by a history of angina, myocardial infarction, congestive heart failure, or arrhythmia were also collected. A cognitive evaluation by a psychiatrist, neurologist, and neuropsychologist as well as lipid screening was done at baseline. Patients were followed at 18-month intervals. The diagnosis of dementia was determined according to DSM IV and other well-published criteria.

**Results:** At baseline, the participants had a mean age of 76.7 years, had 11 years of education, and had total cholesterol of 200 with an HDL of 48. Approximately 16% had diabetes, 60% had hypertension, 19% had heart disease, 9% smoked, and 23% were on lipid lowering therapy. Approximately 66% of the participants were female. The study showed that higher HDL levels were definitely associated with decreased dementia; furthermore, the data showed a threshold, suggesting that participants with HDL >56 were least likely to develop dementia. The data also pointed to higher total cholesterol and LDL levels being associated with decreased incidence of dementia, but this association became nonsignificant when the model was adjusted for vascular risk factors and lipid lowering treatment. The data were then reanalyzed using only participants that received >4.2 years of follow-up and the results did not change.

**Conclusions:** The authors conclude that high levels of HDL are associated with a decreased incidence of dementia. They theorize that HDL may play a role in removing excess cholesterol from the brain, and that a low HDL may lead to vascular dementia. Low HDL is also associated with hyperinsulinemia, which was associated with dementia in this study. Lastly, they hypothesize that low cholesterol and low HDL levels may be part of a prodromal stage of Alzheimer disease.

**Reviewer’s Comments:** Overall, this is a well-done study. Limitations of the study include not adjusting for other risk factors for dementia and not assessing other cardiovascular risk factors, such as a history of stroke, carotid artery stenosis, or other subclinical cardiovascular disease. Lastly, it would have been interesting if lipid panels were checked on each follow-up instead of only at baseline; this may have provided additional information. (Reviewer-Nasiya Ahmed, MD).

**Keywords:** Dementia, HDL Cholesterol, Late-Onset Alzheimer Disease

**Print Tag:** Refer to original journal article
Is IMT Regression Really Useful?


Costanzo P, Perrone-Filardi P, et al:

J Am Coll Cardiol 2010; 56 (December 7): 2006-2020

There is no association between intimal media thickness regression or stability and cardiovascular outcomes.

Background: Carotid intima media thickness (IMT) is associated with cardiovascular disease risks and outcomes. Because it is noninvasive and reproducible, it is an attractive tool for cardiovascular (CV) risk assessment and monitoring of therapy. It has been used as a surrogate end point in many randomized, clinical trials of drug therapies in patients at intermediate or high CV risk. However, there are no compelling data demonstrating that changes in IMT are associated with consistent changes in CV risks.

Objective/Design: The authors of this study report a meta-regression analysis of available randomized trials to determine if reduced progression or regression of IMT is associated with a reduced incidence of CV events in intermediate- to high-risk patients.

Methods: The usual Quality of Reporting Meta-analyses criteria were applied. Trials that lacked the needed outcome information were included if the authors were able to provide the needed data. A total of 9722 articles were identified in the initial search, and 41 of the 85 studies retrieved for more information were included in the analysis. Usual statistical analysis was performed, and publication bias was also accounted for.

Results: The 41 trials included 18,307 participants, with >9000 assigned to a statin and slightly <9000 assigned to another drug or placebo. Follow-up ranged from 0.5 to 5 years, with a mean of 2.4 years. Mean age was 58 years, and 43% of patients were women. In pooled analysis, there was no difference in CV disease events, cerebrovascular (CBV) events, composite outcome, all-cause death, or hard CV events (including cardiac death, myocardial infarction, and stroke based on either delta mean or delta maximum IMT changes from baseline to end of follow-up). In the lipid-lowering trials, however, there was an association between the degree of LDL lowering and coronary heart disease events, composite outcome, and a trend toward benefit in CBV events. Despite this association with LDL lowering, there was no association between IMT changes and LDL lowering.

Conclusions: Favorable IMT changes induced by medical therapies are not associated with a consistent improvement in clinical outcome.

Reviewer's Comments: IMT changes in this meta-analysis do not accurately predict the benefits of therapies with proven beneficial CV effects. As a meta-analysis, the study is hypothesis generating but raises questions on the utility of IMT regression/stability in predicting clinical outcomes in trials. There are many for-profit companies touting the use of IMT in reassessing risk, which could also be called into question by this study. (Reviewer-Karen Stout, MD).

Keywords: Cardiovascular Disease, Carotid Intimal Media Thickness

Print Tag: Refer to original journal article
In patients with known or suspected coronary artery disease, those who can walk at least 9 minutes on a treadmill have a good prognosis even if the test is abnormal or a concomitant nuclear scan is abnormal.

**Background:** Exercise capacity is an important predictor of risk in patients with known or suspected coronary artery disease (CAD). Myocardial perfusion scintigraphy (MPS) provides additional prognostic and diagnostic information compared to exercise alone. Minimum exercise duration of 9 minutes on the treadmill is an accepted threshold for high-risk jobs. There are also defined thresholds for MPS as a screening test.

**Objective:** To compare findings during an exercise test to the results of MPS in patients who can achieve ≥9 minutes of exercise on the Bruce protocol in order to evaluate the risk of developing hard cardiac events.

**Participants/Methods:** Patients were included in the study if they could walk at least 9 minutes and had undergone MPS. Of the 516 patients who met these criteria, 35% had proven CAD. An exercise test was considered high risk if the patient had ≥1 mm ST elevation or ≥2 mm ST depression or the patient described limiting anginal chest pain. MPS was considered high risk if there was ≥1 myocardial segment with reversible hypoperfusion or if the ejection fraction was <40%. Follow-up evaluation looked for all-cause mortality, cardiac death, and nonfatal myocardial infarction. Myocardial revascularization procedures were also recorded.

**Results:** 149 patients had significant ECG changes or limiting chest pain; 69 patients had an MPS consistent with ischemia. Of 367 patients with normal (reassuring) exercise test results, 38 had high-risk MPS. Of 149 patients with a high-risk exercise test, 118 had a reassuring MPS. A total of 498 patients were followed up for a median of 49 months. There were 8 hard cardiac events and 8 noncardiac events. Only 2 of the 147 patients with an abnormal exercise test and 1 of the 67 patients with an abnormal MPS had cardiac events. Most events occurred in patients without abnormal results. Revascularization procedures were performed in 6 of the 8 patients at the time of the acute cardiac events. Revascularization procedures were also performed in some patients with abnormal MPS, but this comprised only a small percentage (9.8%) of patients, so that the majority were treated conservatively, thus allowing for evaluation of long-term outcome. Late (>12 months) revascularization procedures occurred in 4.1% of patients and were unrelated to initial test results.

**Conclusions:** Patients who can walk ≥9 minutes during stress testing using the Bruce protocol have a very low risk of cardiac events regardless of symptoms or ECG changes. Also, there is no additional prognostic value of the MPS in these patients.

**Reviewer’s Comments:** Exercise capacity offers the best determination of prognosis and can be used to screen patients for high-risk jobs. Further work-up is probably not necessary in this patient population. (Reviewer-Marjorie Stanek, MD).

**Keywords:** Nine-Minute Treadmill Test, Myocardial Perfusion Scanning, Prognosis

**Print Tag:** Refer to original journal article
Thrombolytics are underutilized in the patient population aged >80 years.

**Background:** Acute stroke is often treated conservatively in patients aged >80 years due to the fear of side effects such as hemorrhage and even death. However, this has never been proven.

**Objective:** To assess the degree of neurologic damage in those who receive thrombolytic therapy versus those who do not receive therapy after an acute stroke.

**Design:** Nonrandomized, retrospective study.

**Participants:** 5817 patients were gathered from an initial population of 9665 who had an acute stroke and who presented to participating hospitals. Patients included in another study (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) were excluded to avoid using duplicate data. Also, patients with cerebral hemorrhage or stroke of unknown etiology were excluded.

**Methods:** The patients were placed into 2 categories: those who received thrombolytic therapy and those who did not. At each decile of age, the 2 categories were compared based on neurologic function and measurement of functional status.

**Results:** 1585 patients received thrombolytics. The younger patients who received thrombolytics had slightly more severe initial symptoms. In patients aged ≤80 years, the patients who received thrombolytics had better functional outcomes. Also, in those aged >80 years, the patients who received thrombolytics had better outcomes. Everyone from age 51 to 90 years of age did better with thrombolytic therapy.

**Conclusions:** Regardless of age, those who received thrombolytics after an acute stroke had better outcomes. Therefore, age >80 years should not be the sole factor to rule out thrombolytic administration.

**Reviewer's Comments:** Here is more confirmation that what we assume about the oldest old is often wrong and frequently leads to gross undertreatment. The fact that, in some countries, thrombolytics are not approved for patients aged >80 years is shocking. The large population size and the objective functional and neurologic assessments used were strengths of this study. In addition, the population was diverse and from several different countries. However, most patients were from industrialized countries rather than developing countries. In addition, it would have been nice to know the length of time between the onset of stroke symptoms and the infusion of thrombolytic therapy since that would greatly affect the outcomes of the study. I would urge all clinicians to refrain from undertreating geriatric patients, especially those >80 years of age. We all realize the dangers of overtreatment. We need to find the happy medium in which age is only one factor among many to consider for intervention. (Reviewer-Ellyn M. Lee, MD).

**Keywords:** Stroke, Thrombolysis, Age

**Print Tag:** Refer to original journal article
A benchmark for time from hematuria to bladder cancer diagnosis may be within 3 months. This time frame was associated with best bladder cancer survival rates from the SEER database.

Objective: To determine if there is an association between delayed diagnosis and bladder cancer mortality.

Methods: The Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database was queried from 1992 through 2002 for patients diagnosed with hematuria within the year prior to a subsequent diagnosis of bladder cancer. Analysis of bladder cancer-specific and overall survival was then compared between patients diagnosed with bladder cancer sooner versus later.

Results: Compared to patients diagnosed within the first 3 months, patients diagnosed after 9 months had a 34% greater chance of dying from bladder cancer (adjusted hazard ratio, 1.34; 95% CI, 1.20 to 1.50). This difference was consistent even after adjusting for tumor stage and grade.

Conclusions: A delay in the diagnosis of bladder cancer may be just as important for survival as a delay in treatment. Efforts should be undertaken to ensure timely and thorough evaluation of hematuria.

Reviewer’s Comments: There have been a number of studies to date exploring the impact of delays in treatment for bladder cancer. Particularly for muscle invasive disease, delays of >3 months appear to have a significantly harmful effect on survival. In the November 15, 2010, issue of Cancer, Hollenbeck and colleagues explore the impact of delays in the diagnosis of bladder cancer. To do this, they queried the SEER-Medicare linked database for patients who had been diagnosed with hematuria within the year prior to a diagnosis of bladder cancer, presuming that being diagnosed with hematuria should have led to the finding of bladder cancer. Then they divided these patients into respective groups in which the bladder cancer was diagnosed within 3 months of the hematuria, between 3 and 6 months, 6 to 9 months, and after 9 months. Comparing bladder cancer-specific and overall survivals, they were able to show a significantly (34%) increased risk of dying in patients who were diagnosed with bladder cancer after 9 months of a hematuria diagnosis. The difference remained even after adjusting for disease severity (ie, stage and grade), which is remarkable. Perhaps most striking of all was that the risks were the worst for patients with low-risk bladder cancer. Patient with Ta bladder cancer, for example, were twice as likely to die if they had a >9 month delay in diagnosis. There was 1 confusing finding that remains largely unexplained. Regardless of the time-to-diagnosis group, ≥95% of patients had a cystoscopy within 1 month of the hematuria diagnosis. What led to further delays in diagnosis is therefore unclear in patients who had delays. But the survival data are very robust, and appear to clearly indicate that at least in the SEER-Medicare population, delayed bladder cancer diagnosis may be extremely concerning. (Reviewer-Steven E. Canfield, MD).

Keywords: Bladder Cancer, Hematuria, Diagnosis, Outcomes

Print Tag: Refer to original journal article
Children with autism are more likely to display mitochondrial dysfunction, mtDNA overreplication, and mtDNA deletions than found in typically developing children.

**Background:** Isolated case reports have suggested that mitochondrial dysfunction and altered energy metabolism may influence the social and cognitive deficits characteristic of autism, but there are no systematic studies that have explored changes in mitochondrial function or mitochondrial DNA (mtDNA) copy number or deletions.

**Objective:** To evaluate mitochondrial defects in children with clinically defined autism.

**Methods/Participants:** This study utilized a subset of children from the Childhood Autism Risks From Genetics and Environment (CHARGE) study, which explored modifiable factors and markers of biologic dysfunction that potentially provide insight into etiology. Patients were ages 2 to 5 years and were matched with general population controls. Diagnosis of autism was confirmed with standardized tools, and history and physical examinations were performed by a developmental-behavioral pediatrician for each patient. Fresh blood samples were obtained for lymphocytic assay of mtDNA copy number and deletions, rate of hydrogen peroxide production, oxidative phosphorylation capacity, and plasma lactate/pyruvate levels.

**Results:** 10 cases and 10 controls were analyzed. Nicotinamide adenine dinucleotide oxidase activity (a reflection of mitochondrial-dependent oxygen consumption) was reduced more often in children with autism than in normally developing controls. Although there was no difference in lactate levels between groups, plasma pyruvate levels were significantly higher in children with autism, subsequently leading to significantly lower lactate-pyruvate ratios (6 in autistic subjects vs 12 in controls). Rates of hydrogen peroxide production were higher in the lymphocytic mitochondria of autistic children (reflecting an overall increase in cellular oxidative stress). Five of 10 children with autism showed mtDNA overreplication leading to a higher mean mtDNA copy number (ratio of mtDNA to nuclear DNA, 239 vs 179 in controls). Two of 10 children with autism showed mtDNA deletions, although no controls showed deletions in comparable mtDNA segments. Children with mtDNA deletions also had mtDNA replications.

**Conclusions:** Children with autism are more likely to display mitochondrial dysfunction, mtDNA overreplication, and mtDNA deletions than found in typically developing children.

**Reviewer's Comments:** The authors are quick to point out that presence of abnormal lymphocytic mitochondria found here in children with autism may or may not indicate an etiologic role. These defects could be secondary to the unknown event that causes autism, but mitochondrial dysfunction in the high-energy demanding brain could certainly "amplify and propagate brain dysfunction." If evidence of mitochondrial dysfunction in autism accumulates, we may also need to investigate the benefit of nutritional interventions (such as L-carnitine and coenzyme-Q) that are currently used for treatment of more classic presentations of mitochondrial disease. (Reviewer-Alyssa Siegel, MD).
There is no significant risk of birth defects from proton pump inhibitor use in the first trimester.

**Objective:** To determine the risk of birth defects from pre-conception and first-trimester exposure to proton pump inhibitors (PPIs).

**Methods:** In this study from Denmark, the authors used the national health registers to obtain data regarding birth, prescription, and potential confounders (patient history). A cohort of live infants was identified from 1996 to 2008. Women who were pregnant were identified. Prescriptions that were filled by these women for PPI medications between 4 weeks pre-conception up to 12 weeks post-conception were monitored. Birth defects from these pregnancies were documented.

**Results:** The total study cohort included >840,000 births, including 32,000 multiple births. There were 2.6% who had identifiable birth defects. Omeprazole was the most common PPI prescribed. A total of 3.4% of mothers who used a PPI had major birth defects compared to 2.6% of the controlled cohort. Women who used a PPI in the first trimester had no significant risk for major birth defects. There was a slight increase of risk for those mothers who took a PPI within 4 weeks prior to conception. There was no significant risk with an individual PPI medication. Lansoprazole taken within 4 weeks before conception had an increased risk. Post hoc statistical analysis confirmed there was no significant risk for birth defects.

**Conclusions:** There is no significant risk of birth defects from PPI used in the first trimester. Women who expect to become pregnant should consider discontinuing these PPIs if they are trying to conceive.

**Reviewer's Comments:** Women can be reassured that the PPIs have low risks for birth defects. The data showed that there is a slightly higher risk for those mothers who started the medication pre-conception. Since many PPIs are over the counter, these women need to be reminded to check with a doctor prior to taking any medications. For women who are trying to conceive, the avoidance of any non-essential medications, including PPI medications, can help reduce the risk of serious birth defects. (Reviewer-Charles I. Schwartz, MD).

**Keywords:** Birth Defects, Proton Pump Inhibitors

**Print Tag:** Refer to original journal article
Increased media exposure in a 6-month-old child appears to be significantly associated with impaired cognitive and language development at 14 months of age.

**Background:** Despite recommendations that children have no more than 2 hours of media exposure per day, such exposure appears to be increasing overall. Studies show that children from families with a low socioeconomic status (SES) seem to have higher exposure than those from families with higher SES. Studies that link media exposure to adverse events and less optimal development have not been prospective or have focused on children from families with a higher SES.

**Objective:** To examine whether media exposure at 6 months of age is associated with development at 14 months of age.

**Methods/Participants:** This was a study of mother-infant dyads in the Bellevue Project for Early Language, Literacy, and Education Success, a study that attempted to improve development with interventions to encourage shared reading and play. Total duration and content of media exposure were measured at 6 months of age. Media exposure was assessed using a 24-hour recall diary based on a maternal interview. Total duration was measured in minutes. Content was classified into the following categories: educational young child-oriented programs, noneducational young child-oriented programs, older child/adult-oriented programs, and unknown programs. At 14 months of age, cognitive development was measured using the Bayley Scales of Infant and Toddler Development, 3rd edition, Cognitive Scale. Language development was also assessed using the Preschool Language Scale-4. Demographic data and maternal health data were also collected for analyses.

**Results:** Over the 26-month study period, 516 mother-infant dyads were enrolled in the study, and 377 had data collected at 6 months of age. Of these, 259 also had data collected at 14 months of age. Average media exposure at 6 months was 153 minutes a day; only 16% were exposed to <1 hour a day. Even after adjusting for confounding factors, increased media exposure was significantly associated with lower cognitive development (B = -0.15) and lower language development (B = -0.16). When broken down into categories of content, only older child/adult-oriented media was associated with lower development at 14 months of age.

**Conclusions:** Increased media exposure in a 6-month-old child appears to be significantly associated with impaired cognitive and language development at 14 months of age.

**Reviewer’s Comments:** This prospective study showed that increased media exposure in 6-month-old children is associated with decreased language and cognitive development 8 months later. This is troublesome, as the average amount of media exposure in a 6-month-old child was over 2.5 hours. It also seems that older-child/adult-oriented media is the most troublesome. It seems like we keep saying this over and over, but the evidence showing that media exposure in babies, especially inappropriate material, is bad for them. (Reviewer-Aaron E. Carroll, MD, MS).

**Keywords:** Development, Media Exposure

**Print Tag:** Refer to original journal article
**Group Child Care -- Researchers Investigate Risk of Infections**

*Short- and Long-Term Risk of Infections as a Function of Group Child Care Attendance: An 8-Year Population-Based Study.*

Côté SM, Petitclerc A, et al:

Arch Pediatr Adolesc Med 2010; 164 (December): 1132-1137

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Early exposure to large group child care leads to more infections for infants and preschoolers but fewer infections once they become school aged.

**Objective:** To determine whether the frequency of respiratory tract infections (RTIs) with fever, ear infections, or gastroenteritis during the first 8 years of life varies according to age at initiation and type of group child care (GCC).

**Design/Methods:** A cohort of 2023 newborns in Quebec, Canada, was followed up prospectively for 8 years. A total of 61% completed the 8-year study. On a yearly basis, mothers reported the frequency of RTIs, ear infections, and gastroenteritis in the past 3 months from age 1.5 years through 8.0 years of age. Child care was split into 3 categories: home care, "large" GCC (institution-based care), and "small" GCC (home-based care for 3 to 8 children).

**Results:** Compared with home care, children who started large GCC in early preschool (1.5 to 2.5 years) had higher rates of RTIs (incidence rate ratio [IRR], 1.61) and ear infections (IRR, 1.62) during that time, no difference during late preschool years (3.5 to 4.5 years), and fewer RTIs (IRR, 0.79) and ear infections (IRR, 0.57) during the elementary school years (5 to 8 years). Children who started large GCC in late preschool had more RTIs (IRR, 1.47) and ear infections (IRR, 2.36) at that time but were no different by elementary school. Children who started small GCC in early preschool years had more ear infections (IRR, 1.47) in the late preschool period but were also no different by elementary school. Gastroenteritis rates in GCC did not differ from home care at any time period. When the entire study period was examined (1.5 years to 8.0 years), there were no differences in RTIs, ear infections, or gastroenteritis between those in GCC or home care.

**Conclusions:** When compared to home care, early enrollment in large GCC led to more RTIs and ear infections initially but fewer of these infections at elementary school age. Those who started large GCC in late preschool age also had more infections initially, but they did not receive the protective effect during elementary school age. Furthermore, early enrollment in small GCC led to more ear infections initially but no reductions in infections at elementary school age. These findings suggest that enhanced immunity in elementary school age depends upon exposure to many children (large GCC) and initiation of GCC at an early age (before 2.5 years).

**Reviewer's Comments:** This study can help pediatricians to assuage parents' guilt about starting large group day care for their young children. These kids may suffer from more infections initially, but they will have fewer infections at elementary school age. Also, the increased rates of infection incurred at the start of GCC were not dramatically higher (with IRRs between 1.47 and 1.62). The study did not examine the impact of GCC prior to 1.5 years of age, which may have underestimated the infection rates in early preschool. (Reviewer-Daniel Coghlin, MD).

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Keywords: Respiratory Tract Infections, Ear Infections, Gastroenteritis, Child Care

Print Tag: Refer to original journal article
In patients with coronary disease, lowering blood pressure too much may increase future ischemic events.

**Background:** For the general population, a strategy of "lower is better" prevails in the treatment of hypertension. However, there are many who believe in a J- or U-shaped curve with higher event rates at both very low and very high blood pressure (BP) in patients with coronary disease.

**Objective:** To look at the PROVE IT-TIMI 22 subjects in an effort to determine optimal BP following acute coronary syndromes (ACSs).

**Participants/Methods:** 4162 patients with ACS in the preceding 10 days were randomized to pravastatin 40 mg or atorvastatin 80 mg per day. The primary outcome was a composite of time to death, myocardial infarction (MI), unstable angina hospitalization, revascularization, and stroke. The secondary outcome was coronary death, MI, or revascularization after 30 days. Tertiary outcomes consisted of all-cause mortality, coronary death, and nonfatal MI considered separately.

**Results:** The primary outcome was reached in 1000 subjects (24%). The relationship between systolic BP and outcome was J-shaped. Compared with the reference group (systolic 130 to 140 mm Hg), risk increased 4.9 times among those with systolic BP ≤100, while risk increased 1.2-fold with systolic BP >160. Diastolic BP also followed a J-shaped relationship with the primary outcome. Compared with the reference group (diastolic 81 to 90 mm Hg), risk increased 3.7 times among those with diastolic BP ≤60, while risk increased 2.1 times with diastolic BP >100. This J-shaped relationship was more pronounced with follow-up than with baseline BP. A J-shaped relationship was also found for the secondary outcome as well as for cardiovascular mortality and for nonfatal MI.

**Conclusions:** In this population of ACS patients, there was a J-shaped relationship between BP and cardiovascular events. This was true for systolic as well as diastolic BP. Exponential increases in such events were seen at both high and low BP values. BP <110/70 was associated with increased risk of events and may be too low in patients with coronary disease.

**Reviewer's Comments:** As the authors point out, the controversy over the existence of a J-shaped relationship between BP and cardiovascular events has existed for many years. There is persistent concern that lowering BP too far, particularly diastolic BP, in the presence of coronary disease may lead to increased coronary ischemic events. Such a J-shaped relationship has been observed in many studies of hypertension involving coronary disease patients, but is less consistently seen in primary prevention studies involving patients without cardiovascular disease at baseline. It is important to note that observation of a statistically significant relationship does not prove causality. It could be that patients with a poor prognosis mount a lower blood pressure, or it could be that the low BP itself causes the events associated with a poor prognosis. As in the case of blood sugar, "tight control" may not always be best, particularly in patients with significant comorbidities. (Reviewer-Gregg S. Pressman, MD).

**Keywords:** Optimal Blood Pressure, Coronary Disease, J-Shaped Curve

**Print Tag:** Refer to original journal article
Is Dabigatran a Cost-Effective Alternative for Nonvalvular AF?

Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation.

Freeman JV, Zhu RP, et al:


According to this analysis, dabigatran provides additional quality-adjusted life-years at an acceptable incremental cost.

Background: Atrial fibrillation (AF) affects at least 2.3 million Americans and 10% of adults >80 years of age. People with AF have a 5-fold increased risk for ischemic stroke. The annual incidence of stroke in AF patients who are not receiving antithrombotic therapy is 4.5%. Warfarin reduces the relative risk for stroke by two-thirds but has a very narrow therapeutic window. Direct thrombin inhibitors, such as dabigatran, have been shown to be effective to prevent stroke in AF but cost-effectiveness is unclear.

Methods: Statistical decision-making modeling using the published studies of anticoagulation was utilized for analysis. The target population included patients ≥65 years of age with nonvalvular AF, risk factors for stroke (CHADS$_2$ score ≥1 or equivalent), and no contraindications to anticoagulation.

Results: The quality-adjusted life expectancy was slightly better with dabigatran than with warfarin (10.28 quality-adjusted life-years [QALYs] with warfarin, 10.70 QALYs with low-dose dabigatran, and 10.84 QALYs with high-dose dabigatran), while overall costs were slightly higher for dabigatran ($143,193 for warfarin, $164,576 for low-dose dabigatran, and $168,398 for high-dose dabigatran). The results were most influenced by the cost of dabigatran but were relatively stable with adjustments in other features of the model.

Conclusions: In patients ≥65 years of age with nonvalvular AF who are at increased risk for stroke, dabigatran may be a cost-effective alternative.

Reviewer's Comments: Saving people from both the cost and time of warfarin monitoring would be very helpful. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, the dabigatran cohort also had fewer bleeding episode. The cost estimates for this study were based on the price of dabigatran in Great Britain. It would not be surprising if the cost in the U.S. turned out to be significantly higher, thus reducing or even eliminating any potential improvement in cost-effectiveness. In the end though, the cost will likely determine if dabigatran replaces warfarin. Especially if patients use to paying $5 a month or so are asked to spend $10 or twenty times that a month on this new therapy. (Reviewer-Jonathan M. Flacker, MD).

Keywords: Anticoagulation, Atrial Fibrillation, Stroke

Print Tag: Refer to original journal article