DES Associated With Lower Mortality and Rates of MI Compared to BMS

Clinical Effectiveness of Coronary Stents in Elderly Persons: Results From 262,700 Medicare Patients in the American College of Cardiology-National Cardiovascular Data Registry.

Douglas PS, Brennan JM, et al:

J Am Coll Cardiol 2009; 53 (May 5): 1629-1641

DES are associated with better clinical outcomes at 30 months than BMS in a Medicare population.

Background: Drug-eluting coronary artery stents (DES) have dramatically decreased the rates of restenosis and have been rapidly adopted in clinical practice in lieu of bare-metal stents (BMS). Concern about late stent thrombosis (LST) has been raised with DES. Complications, including LST, are infrequent enough that large sample sizes are needed to define the true complication rates.

Objective: To report the results of a study of the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) with the Centers for Medicare and Medicaid Services (CMS) national claims database.

Methods: The ACC-NCDR CathPCI and CMS databases were searched for inpatient percutaneous coronary intervention (PCI) performed from 2004 to 2006 in patients aged ≥65 years. The ACC-NCDR CathPCI database identifies only the index procedure, and the CMS database was used to establish follow-up of up to 3 years. Propensity scores were used to adjust for baseline differences in the treatment groups (BMS vs DES). Multiple subgroups were identified, including indication for PCI, lesion location and length, as well as on- and off-label use of the stent.

Results: 262,700 patients underwent PCI, of which 45,025 received at least 1 BMS and 217,675 received at least 1 DES. There were 21,254 deaths, with more in the BMS group than in the DES group (17.9% vs 12.9% before adjustment; 16.5% and 13.5% after adjustment). Mortality was lower in women and in those with prior PCI or CABG, and higher in those with DM, renal failure, heart failure, or STEMI. MI rates were 8.9 per 100 in BMS and 7.5 per 100 in DES, with a slight increase in MI rates after 12 months in the DES group. In 30 months of follow-up, there was no difference in revascularization rates; however, there were fewer revascularizations in the DES group in the first 12 months, with a rebound to more revascularization in the DES group in 12 to 30 months. There was not a significant difference in the rates of stroke or bleeding. There was a 23% reduction in MI in the DES group, with no increase in late MI.

Conclusions: In a Medicare patient population, DES was associated with lower mortality and lower rates of MI than BMS, with no difference in revascularization over 30 months of follow-up.

Reviewer’s Comments: This enormous study of PCI outcomes helps to shed some light on conflicting data regarding the comparative outcomes of DES and BMS. While there are limitations to database-driven studies such as this, the number of patients affords a window into the complications and outcomes of PCI in the real world and suggests there is a benefit in patients aged>65 years to DES, at least at 30 months. (Reviewer-Karen Stout, MD).

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Keywords: Bare Metal Stent, Drug Eluting Stent, MI Death

Print Tag: Refer to original journal article
Elevated PTH levels, even when normal, are associated with increased CV risk.

**Background:** Patients with elevated parathyroid hormone (PTH) due to primary or secondary hyperparathyroidism have been shown to have increased risk of cardiovascular (CV) disease. The relationship between PTH and CV risk in the general population has not been assessed.

**Objective:** To determine the association of PTH and cardiovascular disease in a population of elderly men. Additionally, as other data have shown other mineral abnormalities to be associated with CVD, the authors evaluated the association of PTH with evidence of abnormal mineral metabolism.

**Design/Methods:** A prospectively identified community-based cohort of men with a mean age of approximately 71 years was evaluated with laboratory data, dietary assessment, physical activity assessment, and CVD as determined by the Swedish Hospital Discharge Registry. The original study is a longitudinal assessment begun in 1970 of all men aged 50 years that were born between 1920 and 1924. The study was intended to evaluate cardiovascular risk and had multiple cycles, with this substudy begun during the third examination cycle. Usual cardiovascular risks were assessed. Laboratory data included PTH levels, and calcium, phosphate, 25 OH vitamin D, and glomerular filtration rate (GFR) were assessed. Cause of death was determined by evaluation of the Swedish Cause of Death Register. Cox proportional hazards regression was done, and PTH levels were evaluated as standard deviations.

**Results:** Higher PTH levels were associated with vitamin D deficiency and prior CVD as well as lower GFR and serum calcium. Of 958 participants, there were 277 deaths and 117 were cardiovascular. In both unadjusted and adjusted models, 1 SD increase in PTH was associated with an approximately 37% increased risk of CV mortality and remained significant when other variables such as BNP and troponin were accounted for (HR, 1.19 for BNP; 1.32 for troponin I). When other factors accounting for mineral metabolism were included, the relationship was only attenuated minimally, and was unchanged once patients with hyperphosphatemia were excluded. Statistical analysis suggested 20% of CV risk in the population was accounted for by elevated PTH (highest quartile vs lower 3 quartiles).

**Conclusions:** Higher levels of PTH, even when normal, were associated with higher risk of CV mortality and accounted for 20% of the population-attributable risk proportion for CV mortality.

**Reviewer's Comments:** Prior studies have demonstrated increased CV risk in patients with overt hyperparathyroidism; however, this is the first study to demonstrate elevated PTH as a CV risk in a community, particularly with patients with normal PTH levels. More research is needed to determine the individual and public health implications, as well as to elucidate the pathophysiologic mechanism of the relationship of PTH in the normal range and increased CV mortality. (Reviewer-Karen Stout, MD).

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Keywords: Parathyroid Hormone, Cardiovascular Disease, Mineral Metabolism

Print Tag: Refer to original journal article
Exercise Can Negate Some of the Cardiovascular Risk of Being Overweight

Prevalence of Cardiovascular Disease Risk Factors Among National Football League Players.

Tucker AM, Vogel RA, et al:

JAMA 2009; 301 (May 27): 2111-2119

Being physically active can reduce cardiovascular risk in overweight individuals.

**Background:** Cardiovascular risks have been associated with obesity and inactivity. Can physical activity mitigate some of the cardiovascular risks of obesity? Many professional football players, or football players on any level, are often overweight but are considered to be physically fit.

**Objective:** To determine the prevalence of cardiovascular risk factors in current NFL players compared to the general population, and to determine the association of these risk factors with player size.

**Design:** Cross-sectional study.

**Methods:** Veteran players on 12 NFL teams were invited to participate. The 12 teams were chosen because they use an air displacement device to assess body composition. Data were collected on each player including age, race, height, weight, blood pressure, lipids, ECG, echocardiogram, blood sugar, % body fat, waist circumference, and other anthropomorphic measures. These data were compared to the Coronary Artery Risk Development in Young Adults (CARDIA) study, a healthy, population-based observational study.

**Results:** 504 players participated in the study, with an average age of 26 years. The NFL players were taller and heavier than those in the population study, but were less likely to smoke and had lower fasting glucose and similar lipids. They did have higher prevalence of pre-hypertension and hypertension than age and ethnically matched controls. In a multivariate analysis adjusting for factors including race and BMI, blood pressure was higher in the NFL group. In linear regression models, BMI was associated with total cholesterol, LDL, fasting blood sugar, triglycerides, and lower HDL.

**Conclusions:** Despite being heavier than the general population, NFL players have lower fasting blood sugar and equivalent lipids, suggesting that physical conditioning can mitigate some of the effects of obesity. The persistent elevation in blood pressure despite matched controls suggests some other factor leading to higher blood pressure, which needs further investigation.

**Reviewer's Comments:** As physicians, we need to continue to emphasize the importance of diet, exercise, and weight control. In ideal circumstances, we would help prevent obesity. It is important to stress to our patients that being active and overweight, even if they do not lose weight, can be helpful in reducing insulin resistance and other cardiovascular risk factors. (Reviewer-Deborah L. Greenberg, MD).

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Keywords: Cardiovascular Risk, NFL Players

Print Tag: Refer to original journal article
This study found that, in patients with non-ST-elevation ACS, early intervention did not improve outcomes as compared to a later approach.

**Background:** In patients with non-ST-elevation myocardial infarction (NSTEMI) and unstable angina, an interventional approach has been found to improve outcomes. However, it remains unclear as to the optimal timing of such interventions.

**Objective:** To determine whether there is a benefit to early intervention, as opposed to a later approach, in non-ST-elevation acute coronary syndromes (ACS).

**Design:** Randomized, parallel-group multicenter trial with blinded adjudication of outcomes.

**Participants:** Patients who presented with unstable angina or NSTEMI within 24 hours of symptom onset were eligible. They also had to have at least 2 of the following 3 criteria: age of ≥60 years, cardiac biomarkers above normal range, or electrocardiographic evidence of ischemia.

**Methods:** Patients were randomized to either an early or late interventional strategy. The early intervention group underwent angiography within 24 hours of randomization. For those in the late group, there was a minimum wait of at least 36 hours. The primary outcome was first occurrence of the composite of death, new MI, or stroke at 6 months. Other areas measured included refractory ischemia and need for repeat interventions.

**Results:** 3031 patients were enrolled, 35% were women, and the average age was 65 years. The median time to angiography was 14 hours in the early group and 50 hours in the late group. There were no significant differences in medications used between the 2 groups. As for the composite of death, MI, or stroke, there was not a significant difference between the early and late group (at either 30 days or 6 months). There was more refractory ischemia in the delayed group, but this was of unclear clinical significance. The Global Registry of Acute Coronary Events (GRACE) score, a cardiac risk score based on numerous easily collected variables, was calculated for each patient. When the one third at highest risk was compared to the two thirds at lower risk, there was a benefit seen for the primary composite outcome.

**Conclusions:** In patients with non-ST-elevation ACS, early intervention did not improve outcomes as compared to a later approach. However, in those patients at highest risk, a benefit was seen.

**Reviewer's Comments:** This study provides some very reassuring news on the care of patients with non-ST-elevation ACS. For those doctors who practice at an institution without angiography capabilities, it appears that a strategy of initial medical management, followed by referral for angiography several days later is completely appropriate. There is a risk for excess refractory angina, but no major differences on hard end points such as death or MI. For those at an institution with cardiac catheterization, it is not necessary to emergently intervene for the majority of patients. However, those at increased risk may benefit from an early intervention. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Acute Coronary Syndromes, NSTEMI, Percutaneous Coronary Intervention, Coronary Angiography

Print Tag: Refer to original journal article
In patients for whom warfarin is unsuitable, the addition of clopidogrel to aspirin reduces the risk of stroke but increases the risk of major bleeding.

**Background:** In patients with atrial fibrillation (AF), warfarin is more effective for stroke prevention than aspirin but carries a higher risk of bleeding.

**Objective:** To assess the risk and benefit of adding clopidogrel to aspirin for stroke prevention in patients with AF.

**Design:** Randomized controlled trial.

**Participants:** 7754 patients with AF for whom warfarin anticoagulation was felt to be unsuitable were evaluated. Participants had to be in AF at enrollment or have had 2 episodes of paroxysmal AF in the preceding month. Patients all took aspirin and were randomized to clopidogrel versus placebo.

**Results:** AF was paroxysmal in 22% of patients. The mean CHADS$_2$ score was 2. After mean follow-up of 3.6 years, the rate of major vascular events (stroke, MI, other systemic embolism or vascular death) was lower with clopidogrel + aspirin than with aspirin alone (6.8% vs 7.9%; RR, 0.89). This difference was primarily due to a lower risk of stroke (2.4% with clopidogrel + aspirin vs 3.3% with aspirin alone; RR, 0.72). However, major bleeding occurred in 2.0% of patients per year with clopidogrel + aspirin versus 1.3% with aspirin alone.

**Conclusions:** In patients for whom warfarin is unsuitable, the addition of clopidogrel to aspirin reduces the risk of stroke but increases the risk of major bleeding.

**Reviewer's Comments:** The authors compared the risks and benefits of clopidogrel and warfarin by comparing the results of this trial with a meta-analysis of warfarin trials. As compared with aspirin, warfarin reduced stroke risk by 38% while increasing the risk of major extracranial bleeding by 70% and major intracranial bleeding by 128%. As compared with aspirin alone, aspirin + clopidogrel reduced stroke risk by 28% while increasing the risk of major extracranial bleeding by 51% and major intracranial bleeding by 87%. They emphasize that warfarin remains the treatment of choice for stroke prevention in AF. The combination of clopidogrel + aspirin offers some additional stroke protection (at the cost of extra bleeding) for patients in whom warfarin is unsuitable. I would particularly consider adding clopidogrel if the contraindication to warfarin was not excessive bleeding risk, but patient preference or difficulty with international normalized ratio monitoring. (Reviewer-Karen A. McDonough, MD).

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Keywords: Atrial Fibrillation, Stroke Prevention, Antiplatelet Agents, Anticoagulants

Print Tag: Refer to original journal article
A polypill may be formulated to conveniently reduce multiple cardiovascular risk factors.

**Background:** There are numerous options to lower the risk of cardiovascular disease; some project large reductions in risk if they are combined.

**Objective:** To test the safety and tolerability of a single pill containing 5 drugs to lower risk of cardiovascular disease.

**Design:** Multicenter randomized controlled trial.

**Participants:** Patients aged 45 to 80 years in India with 1 risk factor for cardiovascular disease.

**Methods:** Patients were assigned to 1 of 9 different groups involving various combinations of the ingredients of the polypill. Some groups got single agents such as aspirin, hydrochlorothiazide, or simvastatin; some received 2, 3, and 4 drug combinations, and 1 group got the entire 5-drug polypill. The doses used were low: aspirin 100 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg, and simvastatin 20 mg. The trial was only 12 weeks in duration, so cardiovascular morbidity and mortality were not end points in this trial. The authors did look closely at whether or not similar blood pressure and lipid outcomes were achieved with the polypill compared to monotherapy, and also looked at safety, tolerability, and dropout rates.

**Results:** As expected, blood pressures went down in the groups receiving an antihypertensive, and it went down more in the groups receiving multiple antihypertensives. In the polypill group, average blood pressure reduction was 7.4 mm Hg systolic and 5.6 diastolic. Groups with a simvastatin-containing regimen showed a reduction in lipids, whereas those without simvastatin did not. LDL reductions were 26 mg/dL in the group on the polypill, and 31 mg/dL in the group on simvastatin alone. This was a statistically significant difference, and the precise reason for it is unclear. Compared to the therapeutic effects, adverse events were remarkably evenly distributed throughout the study groups. Roughly 15% of patients stopped therapy in all groups, although only about 4% were for drug-specific reasons, and the others were for social or unstated reasons. Other adverse effects such as cough, hypotension, hyperkalemia, elevated creatinine, and elevated ALT were all slightly more common than expected but did not show any differences across various study groups.

**Conclusions:** The formulation of this polypill could be conveniently used to reduce multiple risk factors and cardiovascular risk.

**Reviewer's Comments:** For now, I think the most important lesson from this study is that it is possible to combine low doses of multiple medications without seeing a tangible increase in adverse effects. For the future, the implications of this study are even more exciting. Much of the driving force behind the development of a polypill relies on the assumption that the known risk reductions for using individual drugs will be additive when the drugs are given together; if correct, then treatment with a single polypill a day would result in risk reductions between 50% and 80% for many people. (Reviewer-Christopher L. Knight, MD).

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**Keywords:** Risk Reduction, Polypill, Cardiovascular Disease

**Print Tag:** Refer to original journal article
Patients hospitalized for COPD have rates of PE as high as 25%.

Background: Chronic obstructive pulmonary disease (COPD) exacerbations are sometimes unexplained, and COPD patients are at higher risk of thromboembolic disease.

Objective: To determine the prevalence of pulmonary embolism (PE) during COPD exacerbations.

Design: Systematic review and meta-analysis.

Methods: The authors found >2000 papers in their initial search, and narrowed it down to 5 that met all of their inclusion criteria. Of those, 2 studies looked exclusively at inpatients, 2 looked at inpatients and outpatients, and 1 was based in the emergency department. The studies were also heterogeneous in other ways: patients had different risk factors for PE and different severity of COPD in the various studies.

Results: In patients with exacerbations severe enough to warrant hospitalization, 25% were found to have concurrent PE, and 12% had deep vein thrombosis (DVT). In the ED, the rate was much lower: 3.3% for PE and 1.6% for DVT. As one might expect, patients with risk factors were more likely to have PE than those without, but most patients didn't have risk factors. Similarly, certain findings in the clinical presentation were helpful clues—for example, syncope was strongly associated with PE—but were not sufficient to distinguish a high-risk group to image selectively.

Reviewer's Comments: Developing a systematic approach to rule out PE in patients with COPD should be the subject of further, prospective research. However, in the meantime, we should remember that PE is a common cause of worsening dyspnea in patients with COPD who are sick enough to be hospitalized. In patients without an obvious cause of their exacerbation, or patients with risk factors for thromboembolism, we should have a low threshold for ruling out PE. (Reviewer-Christopher L. Knight, MD).

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Keywords: Pulmonary Embolism, Exacerbations

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Assigning patients to PT/OT during interruptions of sedation improves functional outcomes and reduces delirium.

**Objective:** To test whether physical therapy (PT) and occupational therapy (OT) during interruptions of sedation improve outcomes of care in ICU patients.

**Design:** Randomized controlled trial.

**Participants:** 104 patients who had been on mechanical ventilation for <72 hours, were expected to continue for at least another 24 hours, and who were functionally independent at baseline.

**Methods:** Initial intervention was passive range of motion exercises for all limbs each morning. The presence of the physical and occupational therapists was timed to coordinate with daily interruption of sedation. When patients became interactive, they began active range of motion exercises and then started working on transfers and activities of daily living. Patients in the non-intervention group received standard care with PT/OT delivered as ordered by the primary team but without a routine intervention.

**Results:** On average, the intervention group began PT and OT almost a week earlier than the control group. In total, 59% of the intervention group returned to independent functional status at hospital discharge, as compared with 35% for the control group. The number of days with ICU delirium was cut in half from 4.0 in the control group to 2.0 in the intervention group, and the duration of mechanical ventilation was reduced by 2.5 days. The length of stay in the ICU showed a trend toward a reduction, but was not statistically significant (P =0.08). The length of stay in hospital in overall mortality showed no significant differences between the groups.

**Conclusions:** Interruption of sedation and physical and occupational therapy in the earliest days of critical illness is safe and results in better functional outcomes at hospital discharge, a shorter duration of delirium, and more ventilator-free days compared with standard care.

**Reviewer's Comments:** In some ways this study may represent the health care of the future. The intervention reported is not highly technical, not patented, and may not even be particularly expensive, depending on the costs and staffing needs of the therapists. Rather, this represents an effort to improve patient care using better collaboration and better protocols to coordinate existing resources. Although the study did not show a statistically significant impact on length of stay, for the 10 additional patients in the intervention group who were able to walk out of the hospital under their own power, I'm sure these were very significant results. (Reviewer-Christopher L. Knight, MD).

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Keywords: Critical Care, Rehabilitation, Functional Outcomes

Print Tag: Refer to original journal article
Proton pump inhibitors, but not histamine$_2$ blockers, increase the risk for developing hospital-acquired pneumonia in non-ICU patients.

**Background:** Recent studies in outpatient populations suggest that patients using acid-suppressive medications are at higher risk for community-acquired pneumonia. This risk may be highest immediately after initiating these medications. Many patients are started on acid suppressant medication in the hospital. It is not known whether these medications increase the risk for hospital-acquired pneumonia.

**Objective:** To determine if there is an association between acid-suppressive medication and hospital-acquired pneumonia.

**Design:** Prospective pharmacoepidemiologic cohort.

**Methods:** All patients aged ≥18 years admitted for at least 3 days to a large, urban, academic medical center were eligible for inclusion. Any patient cared for in the ICU was excluded. Acid suppression medication exposure included all orders for histamine$_2$ receptor blockers and proton pump inhibitors (PPIs). Diagnoses of hospital-acquired pneumonia were based on discharge ICD-9 codes. A subgroup analysis was planned for those taking histamine$_2$ blockers alone or PPIs alone.

**Results:** The cohort included 63,878 admissions. The average age was 54 years and 63% were women. Patients received acid-suppressive medications in 52% of admissions. Of those, 83% received PPIs and 23% received histamine$_2$ blockers. Hospital-acquired pneumonia occurred in 3.5% of admissions. The adjusted OR for hospital-acquired pneumonia if taking acid-suppressive medication was 1.3 (1.1 to 1.4) compared to those who did not. In subgroup analysis, those taking only histamine$_2$ blockers alone were not at higher risk, but patients taking PPIs alone were (OR, 1.3; 1.1 to 1.4).

**Conclusions:** Patients taking acid-suppressive medications during hospitalization are 30% more likely to develop hospital-acquired pneumonia than patients who are not given these medications.

**Reviewer's Comments:** This study had a few design issues inherent in such a large cohort. The actual clinical information supporting a diagnosis of hospital-acquired pneumonia was not reviewed for each patient, nor was the timing of the acid-suppressive medication in relation to the onset of pneumonia. Despite these issues, this large study adds to the literature that PPIs do carry some associated risks. We should be sure that our patients have reasonable indications for these medications and that the benefits are likely to outweigh the risks.

(Reviewer-Deborah L. Greenberg, MD).

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Keywords: Hospital-Acquired Pneumonia, Acid-Suppressive Medications

Print Tag: Refer to original journal article
Another Treatment Option for PAH?

Tadalafil Therapy for Pulmonary Arterial Hypertension.
Galiè, Brundage BH, et al:
Circulation 2009; 119 (June 9): 2894-2903

Tadalafil at 40-mg daily dose improves some clinical parameters in patients with pulmonary artery hypertension.

**Background:** Pulmonary arterial hypertension (PAH) often leads to right heart failure and death, but there is no known cure. Therapies currently approved to treat PAH are often difficult to take as they are either inconvenient (IV, subcutaneous, or inhaled) or require frequent oral dosing. Tadalafil is a once-daily oral phosphodiesterase 5 inhibitor approved for the treatment of erectile dysfunction.

**Objective:** The authors report a clinical trial of tadalafil in the treatment of PAH.

**Design/Methods:** This double-blind, placebo-controlled trial involved different doses of once-daily tadalafil (2.5, 10, 20, and 40 mg) in patients with PAH. Patients could have a background of treatment with bosentan. The trial was 16 weeks long and was intended to establish tolerability and safety. Patients were >12 years of age with symptomatic PAH. Extremes of distance in a 6-minute walk test were excluded, as was use of any PAH medication other than bosentan. The study was performed in 84 centers in the United States, Canada, Europe, and Japan between 2005 and 2007. The primary end point was 6-minute walk distance at baseline and at week 16, with secondary outcomes of death, heart-lung transplantation, initiation of new PAH medications, atrial septostomy, worsening of functional class, and/or hospitalization due to worsening PAH. The study was funded by Eli Lilly and the “database and all statistical outputs were retained by the sponsor.”

**Results:** 405 patients were randomized to 1 of 5 arms (placebo and the above-mentioned doses of tadalafil). The majority of patients were class II to III, and 53% were on bosentan. While 10- and 20-mg doses were associated with increased 6-minute walk distances, only 40 mg increased the distance to the degree needed for the prespecified statistical significance (33 meters; CI, 11 to 44 meters). There was no change in functional class, whereas time to clinical worsening was improved in the 40-mg group. Adverse events occurred across all treatment groups, and there were 3 deaths (1 in the placebo arm and 2 in the treatment arms). There were no changes in laboratory data.

**Conclusions:** Tadalafil 40 mg once daily provides a favorable efficacy-to-safety profile and offers clinically meaningful therapy as an addition to currently used medications to treat PAH.

**Reviewer’s Comments:** The success of sildenafil as a PAH treatment seems to have inspired this trial of tadalafil, which offers the advantage of once-daily dosing. As is often the case in PAH trials, the “clinically meaningful” improvement often seems spartan compared to the cost of the medication. An additional 33 meters in a 6-minute walk test is statistically significant, but whether it will be a cost-effective therapy remains to be seen. A survival benefit was not demonstrated in this small trial, but would need to be assessed in a larger study. (Reviewer-Karen Stout, MD).

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Keywords: Pulmonary Arterial Hypertension, Tadalafil

Print Tag: Refer to original journal article
Obstructive sleep apnea is common after bariatric surgery, despite significant weight loss. In this meta-analysis, 62% of patients had moderate or severe obstructive sleep apnea after bariatric surgery.

**Background:** Bariatric surgery reduces the morbidity and mortality associated with severe obesity. In addition to well-documented reductions in the risk of diabetes and overall mortality, previous studies have shown that bariatric surgery results in reductions in obstructive sleep apnea (OSA). There have been conflicting studies on whether weight loss associated with bariatric surgery is likely to result in a cure of OSA.

**Objective:** The current study is a meta-analysis of studies of OSA severity before and after bariatric surgery.

**Design/Methods:** The authors performed a literature search for English-language studies that included polysomnographic measures of OSA severity before and at least 3 months after bariatric surgery. Data abstracted from the studies included body mass index (BMI) and apnea-hypopnea index (AHI), patient demographics, and time of follow-up polysomnography after bariatric surgery. The authors used standard statistical measures to assess for study heterogeneity and publication bias. Individual patient data were available for a subset of study subjects. The meta-analysis was based on a random effects model.

**Results:** A total of 2309 studies were identified by their intentionally broad literature search, although most studies were screened out. Ultimately, a total of 12 manuscripts representing 342 patients were included in the meta-analysis. Only 5 of the 12 studies were prospective. The studies demonstrated a high degree of heterogeneity, but there was no evidence of publication bias. Following bariatric surgery, the average BMI decreased from 55.3 kg/m² to 37.7 kg/m² (95% CI, 36.6 to 38.8). The average AHI decreased significantly following bariatric surgery, but remained, on average, in a moderately severe range. Presurgical AHI was 54.7 events/hour, and postsurgical AHI was 15.8 events/hour (95% CI, 12.6 to 19.0).

**Conclusions:** Although bariatric surgery resulted in substantial weight loss and improvements in sleep-disordered breathing, on average, patients remained obese following bariatric surgery (BMI, 37.7) and continued to have moderately severe OSA (average AHI, 15.8 events/hour). Overall, 62% of patients had moderate or severe OSA after bariatric surgery.

**Reviewer’s Comments:** This study suggests that most patients with OSA prior to bariatric surgery will continue to have at least moderate OSA after surgery. There are 2 important messages from this study. (1) We and our patients should not expect bariatric surgery to cure OSA. (2) We should consider repeat polysomnography in patients with OSA prior to bariatric surgery before considering cessation of therapies such as CPAP. This is particularly important, as patients may feel substantially more energetic as they lose weight, which may lead to the misapprehension that they no longer need CPAP. (Reviewer-Paul R. Sutton, PhD, MD).
In patients with diabetes mellitus type and CAD, an early interventional approach does not improve clinical outcomes compared to medical management alone.

**Background:** Patients frequently present with concomitant diabetes and coronary artery disease (CAD), and the optimal management of each remains unclear.

**Objective:** The Bypass Angioplasty Revascularization Investigation 2 Diabetes had 2 goals. First, with respect to CAD, it sought to explore the role of early revascularization. Second, it compared insulin sensitization, using metformin and/or thiazolidinediones, with insulin provision (sulfonylureas and/or insulin) on cardiovascular outcomes.

**Design:** Multicenter randomized 2 x 2 factorial design.

**Participants:** Patients with diabetes who were referred for angiography were considered. If the diagnosis of significant CAD was confirmed, patients had to be a candidate for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to be eligible. Exclusion criteria included need for urgent revascularization, renal insufficiency, very poor glycemic control, or PCI/CABG in the previous 12 months.

**Methods:** The responsible physician determined whether PCI or CABG would be more appropriate. Then, within both the recommended CABG and PCI groups, patients were randomized to either medical therapy alone or to continue on to the chosen revascularization strategy. At that point, there was a second step of randomization. In each of these 4 arms, patients were then randomized to a strategy of insulin sensitization or insulin provision. The primary end point was overall survival, with a secondary outcome of a composite of major cardiovascular events.

**Results:** 2368 patients were included, with average follow-up of 5.3 years (93% completed the study). At 5 years, there was no significant difference in overall survival or major cardiovascular events when comparing the revascularization and medical management approaches or between the insulin sensitization and insulin provision arms. In looking at those in whom PCI was recommended, there were no differences between the interventional and medical treatment arms. In those in whom CABG was recommended, there were no survival differences between those who underwent CABG and those treated medically. However, in this group, undergoing CABG did significantly reduce the rate of major cardiovascular events.

**Results/Conclusions:** In patients with diabetes mellitus type 2 and CAD, an early interventional approach did not improve clinical outcomes when compared to medical management alone. In addition, there were no significant differences between insulin provision and insulin sensitization approaches.

**Reviewer's Comments:** This study adds to our understanding of 2 common clinical questions. First, an aggressive interventional approach to CAD did not fare any better than intensive medical management. Revascularization for stable coronary disease continues to be an effective tool for reducing angina, but its clear benefits on harder cardiovascular end points are reserved for acute coronary syndromes and high-risk coronary disease. As for the management of diabetes, it did not appear to make a difference as to which approach was followed. Therefore, I believe it is difficult to make a strong statement on treatment choices. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Coronary Artery Disease

Print Tag: Refer to original journal article
Ezetimibe at a dose of 5 mg seems to be just as good as 10 mg for lowering cholesterol.

**Background:** The only dose available for ezetimibe is 10 mg, despite the fact that, in clinical development trials, 5-mg dosing did a good job of lowering cholesterol levels. Given the high cost of ezetimibe, if a 10-mg tablet could be split and still be just as effective as the full tablet, it would lead to significant cost savings. **Objective:** To evaluate whether patients receiving 5 mg of ezetimibe had similar lipid lowering as patients receiving 10 mg. **Design/Methods:** The study was a randomized trial of patients at a Veterans Affairs medical center who were taking ezetimibe and met the criteria for compliance (taking >75% of doses). A total of 130 patients were screened for eligibility, with 39 patients being eligible and 36 completing the study. Patients were randomized to continue on 10 mg of ezetimibe or to switch to one-half a tablet (5 mg) daily. Lipid panels were collected at baseline and after 4 weeks of therapy. **Results:** No difference was found in LDL cholesterol for patients randomized to receive 5 mg of ezetimibe. The mean LDL cholesterol for patients was 96 before switching to 5-mg dosing and 97 after the switch (at 4-week follow-up). **Conclusions:** There appears to be no clinical difference in the lipid-lowering abilities of 5 mg versus 10 mg of ezetimibe. **Reviewer's Comments:** This information is helpful. Given the high cost of ezetimibe, splitting the pills can lead to a 50% cost savings without decreasing lipid-lowering efficacy. The question still remains whether ezetimibe has an important clinical role. The ENHANCE trial did not show any improvement in carotid intima media thickness despite good LDL lowering with the addition of ezetimibe to simvastatin. Studies with clinically relevant end points are still pending. (Reviewer-Douglas S. Paauw, MD).
Do Statins Prevent VTE?

*A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism.*

Glynn RJ, Danielson E, et al:


Statins reduce the rates of symptomatic venous thromboembolism in patients with elevated HS-CRP.

**Background:** It is well established that statins reduce vascular events related to arterial disease. There remains controversy whether statins have any significant impact on venous disease. The JUPITER trial was a large trial investigating both these issues.

**Objective:** To determine if rosuvastatin reduces the rate of venous thromboembolism (VTE).

**Design:** Multicenter, randomized, double-blind, placebo-controlled trial.

**Participants:** Men ≥50 years of age and women ≥60 years of age without previous cardiovascular disease were eligible. LDL cholesterol had to be <130 mg/dL, and high-sensitivity C-reactive protein (HS-CRP) had to be ≥2 mg/dL. Exclusion criteria included the presence of cancer in the last 5 years, diabetes, and/or the use of postmenopausal hormone therapy.

**Methods:** Patients were randomized to either rosuvastatin 20 mg daily or matching placebo. They were followed up at regular intervals for identification of episodes of VTE (either deep venous thromboembolism or pulmonary embolism). Episodes of VTE were considered provoked if there had been trauma, surgery, or hospitalization within the prior 3 months as well as a diagnosis of malignancy.

**Results:** The study was actually terminated early at the recommendation of the data and safety monitoring board due to benefits seen in reducing combined cardiac and cerebrovascular event rates. More than 17,000 patients were enrolled from around the world, with 38% women, and 32% aged ≥70 years. Over a median follow-up of 1.9 years, symptomatic VTE occurred in 94 participants, 34 in the rosuvastatin group versus 60 with placebo. This translated into 1.8 events/1000 person-years versus 3.2 events/1000 person-years, for a hazard ratio of 0.57 (95% CI, 0.37 to 0.86; \(P = 0.007\)). Rates were similarly reduced in both provoked and unprovoked cases of VTE.

**Conclusions:** In generally healthy participants with elevated HS-CRP and relatively good LDL values, the use of rosuvastatin led to a small but statistically significant reduction in rates of VTE.

**Reviewer’s Comments:** The JUPITER trial, in which rosuvastatin was shown to decrease the rates of important cardiovascular events in patients with elevated HS-CRP, has certainly been a major topic of discussion. This study now adds a bit to that by showing modest reductions in cases of symptomatic VTE as well. The authors go on to combine these outcomes and estimate that the number needed to treat for 4 years to prevent either an episode of VTE or combined cardiovascular end point is 26. That said, when specifically looking at the reductions in episodes of VTE, the numbers here are quite small, making the clinical relevance questionable. It is definitely interesting as we continue to better understand the effects of statins and causes of unprovoked VTE. However, the role of statins will continue to be in reducing cardiovascular events, and, perhaps as an offshoot, we'll also see modest reduction in VTE. (Reviewer-Mark E. Pasanen, MD).

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**Keywords:** Venous Thromboembolism, Statins

**Print Tag:** Refer to original journal article
Tamsulosin Affects Outcomes in Cataract Surgery

**Association Between Tamsulosin and Serious Ophthalmic Adverse Events in Older Men Following Cataract Surgery.**

Bell CM, Hatch WV, et al:


**Tamsulosin is associated with double the risk of adverse eye outcomes after cataract surgery.**

**Design:** The commonly prescribed α-blocker tamsulosin treats benign prostatic hypertrophy by relaxing smooth muscle in the bladder neck and prostate. Receptors for the drug are also present in the iris dilator muscles of the eye. During cataract surgery, those taking tamsulosin have less pupillary dilation and what the ophthalmologists call intraoperative floppy iris syndrome, which makes surgery more technically difficult.

**Objective:** To assess whether tamsulosin therapy increases the risk of adverse eye outcomes following cataract surgery.

**Design/Participants:** Case-control study involving all men aged ≥65 years who had cataract surgery between 2002 and 2007 in Ontario, Canada.

**Methods:** Cases were identified by a physician service claim within 14 days of cataract surgery for a procedure used to treat a complication: dislocated lens extraction (for lens displacement or lens fragment), air or fluid exchange (for retinal detachment), and vitrectomy, vitreous aspiration or vitreous injection (for suspected endophthalmitis). For each case, 4 controls with the same age, surgeon, and year of surgery were identified. Exposure to tamsulosin and other α-blockers, including prazosin, doxazosin, terazosin, and alfuzosin was determined from pharmacy records.

**Results:** 3.7% of patients had been exposed to tamsulosin within 14 days and 11% to other α-blockers; 284 patients (0.3%) had at least 1 procedure due to an adverse event within 2 weeks of cataract surgery: 175 for lost lens or lens fragment, 35 for retinal detachment, and 100 for suspected endophthalmitis. Of case patients, 7.5% versus 2.7% of control patients were recently exposed to tamsulosin. The adjusted odds ratio for adverse events in tamsulosin-treated patients was 2.3. There was no increased risk of adverse events for those treated with other α-blockers.

**Conclusions:** Tamsulosin was associated with more than double the risk of adverse eye outcomes in patients having cataract surgery.

**Reviewer’s Comments:** An editorial in the same issue of the JAMA says that it isn’t clear how long after discontinuing tamsulosin that the risk of complications decreases, and it may not ever completely return to baseline. Pharmacological and mechanical strategies for dealing with the “floppy iris” are being developed. Overall, the risk of these adverse events is low and about doubles with tamsulosin. However, cataract surgery is widely perceived as very safe, and these complications may be vision threatening, so it’s important that men taking tamsulosin ensure that their ophthalmologists know. (Reviewer-Karen A. McDonough, MD).

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Keywords: Cataracts, Tamsulosin

Print Tag: Refer to original journal article
Patients treated with cholinesterase inhibitors are more likely to have syncope and bradycardia than untreated patients with dementia.

**Background:** Cholinesterase inhibitors, including those used to treat dementia, increase vagal tone with the potential to cause bradycardia and syncope.

**Objective:** To assess the risk of syncope attributable to cholinesterase inhibitors used for the treatment of dementia.

**Design:** Population-based cohort study in Ontario, Canada.

**Participants:** Community-dwelling patients aged ≥65 years with a diagnosis of dementia made in the last 5 years.

**Methods:** Patients were identified based on a review of very reliable administrative and drug benefit databases. All patients had been diagnosed with dementia in the previous 5 years, had seen a physician in the previous 3 months, and had no hospitalizations for syncope in the past year. Residents of long-term care were excluded. The cholinesterase cohort included 19,803 patients who had been prescribed donepezil, galantamine, or rivastigmine within the past year (13,641 patients treated with donepezil, 3448 with galantamine, and 2714 with rivastigmine). The control cohort included 61,499 patients who had never received any of these drugs. Outcomes measured were hospital visits for syncope, bradycardia, or atrioventricular block, pacemaker insertion, or hip fracture. These outcomes were compared for the cohorts as a whole, and then for cholinesterase patients and controls matched for co-morbidities and for a propensity score incorporating all variables affecting syncope risk. **Results:** The cholinesterase group was at moderately increased risk of all outcomes: hazard ratio of 1.76 for hospital visit for syncope, 1.59 for bradycardia, 1.49 for pacemaker, and 1.18 for hip fracture. This increase in risk was seen in the cohort as a whole, as well as in the co-morbidity and propensity-matched cohorts.

**Conclusions:** Cholinesterase inhibitor use is associated with an increased risk of syncope, bradycardia, pacemaker placement, and hip fracture.

**Reviewer’s Comments:** The authors suggest that the risk of adverse outcome be weighed against the generally modest benefit of this class of drugs. I believe hip fracture is the most significant of the reported events, and the increased risk just reached statistical significance. I would use this study to argue against prescribing the drugs for patients unlikely to benefit (ie, mild cognitive impairment without dementia or severe dementia). I will also be more likely to stop using them when I see patients with syncope or near syncope, to avoid subsequent hip fracture. (Reviewer-Karen A. McDonough, MD).

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**Keywords:** Dementia, Vagal Tone, Bradycardia, Syncope

**Print Tag:** Refer to original journal article
How Long Should We Suppress Androgens in Prostate Cancer?

Duration of Androgen Suppression in the Treatment of Prostate Cancer.
Bolla M, de Reijke TM, et al:


In patients with locally advanced prostate cancer treated with radiotherapy, 3 years of androgen suppression is better than 6 months.

**Background:** In patients with locally advanced prostate cancer treated with radiotherapy, androgen suppression for at least 2 years has been shown to improve survival. However, many patients have significant side effects from this treatment, and it is unclear whether shorter-term therapy is equally beneficial.

**Objective:** To determine if short-term androgen suppression would have similar overall survival to longer treatment.

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

**Participants:** Patients diagnosed with prostate cancer and no evidence of distant metastases were eligible. For those with smaller tumors, there also had to be evidence of focal nodal spread, while those with larger tumors were eligible regardless of nodal status. In addition, prostate specific antigen (PSA) had to be <40 times the upper limit of normal.

**Methods:** After external beam radiotherapy and 6 months of androgen suppression (with both a luteinizing hormone-releasing hormone [LHRH] analogue and an anti-androgen), patients in whom there had not been progression were randomized to either no further hormonal treatment or further androgen suppression with just the LHRH analogue for 2.5 years. The primary outcome was overall survival, with secondary measures including survival free of clinical or biochemical progression.

**Results:** 970 men underwent randomization, with a median age of 69 years and a follow-up for 6.4 years. Most men (92%) had T2c to T4 disease without nodal involvement. Gleason scores were evenly distributed, and the median PSA was 18 ng/mL. As for the primary outcome, at 5 years, overall mortality was 15% with the longer treatment compared to 19% with short-term treatment. In the long-term suppression group, the major side effects were hot flushes (>3 times daily in 39%) and gynecomastia (18%). Overall quality-of-life scores were similar, but sexual problems were more common in the treatment group. No significant differences were seen in cardiovascular outcomes, a potential concern of continued androgen suppression.

**Conclusions:** In patients with locally advanced prostate cancer treated with radiotherapy, 3 years of androgen suppression is superior to 6 months.

**Reviewer's Comments:** In patients with prostate cancer, I have had a number of patients complain about the side effects of continued androgen suppression. This study helps frame the discussion of the importance of continuing with treatment. It appears that we probably need to treat only about 25 men with the longer treatment regimen to prevent 1 death. It also helps decrease concerns of cardiovascular and metabolic effects of longer-term androgen suppression (compared to shorter treatment). So far, armed with this new set of evidence, I will try to support these patients through longer-term treatment. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Prostate Cancer, Androgen Suppression

Print Tag: Refer to original journal article
Patients with advanced stage lung cancer can get a tiny increase in life expectancy by adding cetuximab to standard chemotherapy, but the cost is staggering.

**Background:** Cetuximab (Erbitux) is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), and has shown potential efficacy for non-small cell lung cancer (NSCLC) in bench research.

**Objective:** To establish the value of cetuximab in treatment of advanced lung cancer.

**Design:** Open-label, randomized, controlled trial.

**Participants:** 1125 patients ≥18 years of age with either stage IIIIB with pleural effusion or stage IV NSCLC and no prior chemotherapy.

**Methods:** Patients were treated with up to six 3-week cycles of cisplatin and vinorelbine per defined protocols. The intervention group received 400 mg/m2 of cetuximab on day 1 and then 250 mg/m2 weekly. The cetuximab was continued until either disease progression or unacceptable toxicity occurred. The primary end point in the trial was overall survival. Secondary end points included progression-free survival, overall response, quality of life, and safety.

**Results:** This study found that median survival increased from 10.1 months to 11.3 months in the treatment group, a difference that was statistically significant, with a $P$ value of 0.044 when expressed as a hazard ratio. No significant difference was noted in quality of life or safety, although the investigators noted the return rate of their quality-of-life questionnaires was poor.

**Reviewer's Comments:** According to my favorite drug reference, Erbitux costs $570 per 100-mg vial. For a patient with an average body surface area of 1.73 m2, the dosing used in this study costs roughly $2500 per week. For the average patient, this adds up to roughly $100,000 for 1 extra month of survival. As primary care physicians, we are not likely to be infusing Erbitux and may not even be in the position to make decisions about whether or not it is used. However, our patients will, and as a physician with whom they have a long-standing relationship, we can help them in their decision making not only in the crucial moment, but also over time, by helping focus on their values rather than simply their survival. It is too easy to ask ourselves "what we would want to be done if it was our mother" and rationalize excess. We need to start asking what we would want to be done if it was our mother's $100,000. (Reviewer-Christopher L. Knight, MD).

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Keywords: Lung Cancer, Cetuximab

Print Tag: Refer to original journal article
Using blood samples obtained as part of the Prostate, Lung, Colon, and Ovary Cancer Screening Study, authors from the Mayo clinic and the National Cancer Institute found that MGUS precedes virtually all incident cases of multiple myeloma.

**Background:** Monoclonal gammopathy of uncertain significance (MGUS) is a common premalignant condition with an estimated prevalence of 3.2% among the white American population ≥50 years of age. Over long-term follow-up, patients with MGUS appear to be at increased risk for progressing to multiple myeloma (MM) or other malignant myeloproliferative disorders, with a risk approaching 25% at 25 years of follow-up. Although it is well established that MGUS may precede MM, it remains unclear whether MGUS is a common, or even obligatory, precursor to the development of MM.

**Objective:** To determine whether MGUS is a common antecedent to MM.

**Methods:** This was a substudy of the National Institutes of Health-sponsored Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. In this study, >150,000 subjects between 55 and 74 years of age were enrolled and randomized to a cancer screening protocol versus usual medical surveillance. For the current study, the authors retrospectively identified 106 patients who were diagnosed with incident MM during the course of the cancer screening study. The authors analyzed banked blood samples from patients diagnosed with MM for the presence of monoclonal protein (M-protein) levels prior to the diagnosis of MM. Immunofixation was performed to determine free kappa and lambda light chain (FLC) levels. MGUS was defined as elevated FLC >2 years prior to the diagnosis of MM. By requiring elevated FLC for at least 2 years prior to MM diagnosis, the authors excluded patients with prevalent MM at study enrollment.

**Results:** Of 106 patients diagnosed with MM, 71 had stored blood samples at least 2 years prior to diagnosis. The prevalence of MGUS was 100%, 97.9%, 100%, and 82.4% at 2, 4, 6, and 8+ years prior to diagnosis with MM. The 95% confidence intervals (CIs) around these point estimates were relatively tight, with a lower limit of 86.3% and 56.3% at 6 and 8+ years, respectively, prior to diagnosis with MM.

**Conclusions:** MGUS was present for up to 6 years in virtually all patients diagnosed with MM, and most patients have MGUS for ≥8 years prior to diagnosis with MM.

**Reviewer's Comments:** The authors concluded that MGUS is a nearly obligatory premalignant condition in the development of MM. This study suggests that MGUS is necessary, but not sufficient for the development of MM. Future studies will better define the features and molecular changes of MGUS that predict increased risk of progression, and therefore, might warrant more frequent laboratory monitoring. It also shines a bright light on MGUS as a target of molecular and genetic research now that it seems to be essential for the development of MM. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: MGUS, Multiple Myeloma

Print Tag: Refer to original journal article
In a fair quality meta-analysis, proton pump inhibitors given during pregnancy were not associated with fetal risk.

**Background:** Heartburn (HB) and reflux symptoms are extremely common in pregnancy, ranging from 40% to 85%, and often require pharmacotherapy with antacids, histamine H2 blockers, or proton pump inhibitors (PPIs). The Food and Drug Administration (FDA) considers PPIs as "class B" for use in pregnancy, indicating that animal and/or human studies have not identified any fetal risk associated with their use.

**Objective:** To conduct a meta-analysis of available studies evaluating PPIs during pregnancy.

**Methods:** Eligible studies included use of PPIs during at least the first trimester of pregnancy, a comparison group not exposed to PPIs, and fetal outcomes. The fetal outcomes of note were congenital malformations, spontaneous abortions, and premature delivery. The quality of the articles included in the meta-analysis was estimated using a validated scale (Downs-Black scale). Publication bias was evaluated by funnel plot. Meta-analysis was performed using a random effects model.

**Results:** 60 articles were reviewed, and ultimately, 6 articles and 1 as yet unpublished abstract were included in the meta-analysis. Four of the studies were prospective cohort studies and 3 were retrospective studies. The studies were all of "fair" quality according to the Downs-Black scale. The funnel plot did not suggest any publication bias, and there was no statistical heterogeneity among the studies, suggesting that it was reasonable to combine them for meta-analysis. A total of 1530 exposed subjects and 133,410 unexposed controls were included in the meta-analysis. The odds ratio (OR) for the incidence of congenital malformations after exposure to PPIs was 1.12 (95% CI, 0.86 to 1.45). The OR for pre-term deliveries was 1.13 (95% CI, 0.96 to 1.33) and the OR for spontaneous abortions was 1.29 (95% CI, 0.84 to 1.97), although this was based on 2 studies with only 524 exposed and 981 nonexposed controls.

**Conclusions:** First trimester use of PPIs was not associated with an increased risk of major congenital malformations, pre-term deliveries, or spontaneous abortions.

**Reviewer's Comments:** PPIs were approved by the Food and Drug Administration for clinical use in 1989 and have become one of the most commonly prescribed classes of prescription drugs. While generally safe, a number of safety concerns have arisen from post-marketing data. PPIs may be associated with an increased risk of community-acquired pneumonia, *Clostridium difficile* infection, and, with prolonged use, hip fracture. Thus, this meta-analysis supports the expert consensus that PPIs are safe for use in pregnancy, but only time and further clinical experience will definitively answer the question. Furthermore, the adage "garbage in, garbage out" pertains with any meta-analysis, and the conclusions of this study were based on a total of 7 articles, all of which were regarded as being of only fair quality, and one of which contributed 43% of the patients who received PPIs and 88% of the controls. (Reviewer-Paul R. Sutton, PhD, MD).

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**Keywords:** Pregnancy, Proton Pump Inhibitors

**Print Tag:** Refer to original journal article
There is no clear benefit to antioxidant supplementation in preventing cognitive decline in women at risk of, or with, vascular disease.

**Background:** Vascular disease is associated with cognitive decline and dementia, with some data suggesting oxidative damage may be important in the pathophysiology. The role of antioxidants in preventing cognitive decline or dementia is poorly studied.

**Objective:** The authors report a substudy of the Women's Antioxidant and Cardiovascular Study focusing on the impact of antioxidants in cognitive function of women at risk of, or with, vascular disease.

**Design:** A 2 x 2 x 2 factorial design, randomized, placebo-controlled study of vitamin E, vitamin C, and beta-carotene as secondary prevention of vascular disease.

**Participants/Methods:** Participants are women professionals, enrolled in 1995 to 1996, who were ≥40 years of age and had documented cardiovascular disease (CVD) or ≥3 coronary artery disease (CAD) risk factors. The majority of the 2824 participants were white (94%). Women were randomized if they did not have active liver disease, cancer in the last 10 years, or chronic renal failure. They also had to demonstrate, good compliance with a 3-month placebo run-in and were willing to avoid other vitamins. The cognitive substudy was begun a mean of 3.5 years after randomization in women ≥65 years of age. Cognitive function was assessed by phone interview. Tests measured general cognition, category fluency, and verbal memory. Verbal memory is associated with the development of Alzheimer's dementia. The primary end point was change over time of an aggregate score of all tests, and the secondary end point was change in verbal memory. The doses used were 600 IU of vitamin E every other day, 500 mg/day of vitamin C, and 50 mg every other day of beta carotene.

**Results:** The group taking vitamin C had borderline significantly higher composite scores at the final assessment than did the placebo group. There was no difference in the vitamin E and beta carotene groups compared with placebo. There was also no difference in the patients on different combinations of 2 of the antioxidants and only a borderline significant improvement in those women taking all 3 of the supplements compared with placebo. A suggestion of a late benefit of vitamin C was seen in secondary analysis, however, this was of borderline significance. There was also a borderline significance to beta carotene supplementation in patients with low dietary intake of carotenoids.

**Conclusions:** Supplementation with antioxidants does not slow the progression of cognitive decline in patients at risk of, or with, CVD. Further study is needed to evaluate the possibility of late effects of vitamin C and the benefit of beta carotenoids in patients with low dietary intake of carotenoids.

**Reviewer's Comments:** While oxidation continues to be demonstrated as an important part of the pathophysiology of CVD, cognitive decline, and dementia, there is not yet compelling evidence that supplementation with antioxidants is beneficial in preventing or slowing disease progression. (Reviewer-Karen Stout, MD).

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Keywords: Vitamin E, Vitamin C, Beta Carotene, Vascular Dz, Dementia

Print Tag: Refer to original journal article
CT colonography is not as accurate as colonoscopy in detecting high-risk lesions.

**Background:** Adherence to current colon cancer screening recommendations with colonoscopy is not optimal. CT colonography, because it is less invasive, may be more acceptable to patients and thus lead to increased screening adherence. The accuracy of CT colonography as a screening test for colon cancer in individuals at increased risk is not known.

**Objective:** To compare CT colonography to colonoscopy as a screening test for colon cancer in a high-risk patient population.

**Design:** Multicenter cross-sectional study.

**Methods:** Patients with a positive fecal occult blood test (FOBT) (age range, 59 to 69 years), a first-degree relative with colorectal cancer (CRC) diagnosed prior to age 60 years (age range, 40 to 65 years), or a personal history of colonic adenoma (age range, 18 to 70 years) were enrolled in the study and underwent CT colonography and colonoscopy on the same day. The primary end point was the sensitivity and specificity of CT colonography in detecting colonic adenomas or cancers of at least 6 mm (ie, advanced neoplasia) compared to colonoscopy. Colonic polyps were removed at the time of colonoscopy and were considered high-risk if they were ≥10 mm, ≥20% villous, or had significant dysplasia.

**Results:** 12 centers in Italy and 1 center in Belgium provided 937 patients for analysis. The prevalence of advanced neoplasia was 7.5% in patients referred for a family history, 11.1% in patients with prior polyps, and 50.2% in those with positive FOBT. The test characteristics for CT colonography in detecting advanced neoplasia compared to colonoscopy was: sensitivity 85.3%; specificity 87.8%; positive predictive value, 61.9%; and negative predictive value, 96.3%. The sensitivity for detecting high-risk lesions was 90.8% and 95.1% for cancer.

**Conclusions:** CT colonography compares well with colonoscopy when used as a screening test for colon cancer in high-risk individuals. If CT colonography is more acceptable to patients and thus more patients undergo recommended screening, then the overall detection rate of CRC would be improved.

**Reviewer's Comments:** Although CT colonography is perceived by patients to be a more acceptable test, it clearly is less effective in detecting high-risk polyps and actual colon cancer even in patients at elevated risk. For now, we should try to better educate patients about the benefits of colon cancer screening with colonoscopy. (Reviewer-Deborah L. Greenberg, MD).

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Keywords: CT Colonography, Advanced Neoplasia, Diagnostic Accuracy

Print Tag: Refer to original journal article
Patient self-management of musculoskeletal pain is an important aspect of treating comorbid depression and pain.

**Background:** Pain and depression are common outpatient primary care symptoms and often coexist.

**Objective:** To determine if the combination of antidepressant medication and pain self-management improve both depression and pain in adult primary care patients compared to usual care.

**Design:** Randomized clinical trial.

**Methods:** The Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study randomized outpatients with depression and chronic low back, hip, or knee pain to usual care or a 3-step treatment program. The 1-year program was composed of 12 weeks of optimal antidepressant therapy, then 12 weeks of a pain self-management program, followed by a 6-month continuation phase. Patients were recruited from community-based and Veterans Administration (VA) medical clinics in Indianapolis. There were a fair number of exclusion criteria. The primary end point was scores on the 20-item Hopkins Symptom Checklist (HSCL-20) to assess depression and the Brief Pain Inventory (BPI) scale to assess pain. Patients were considered "responders" if they had a 50% reduction in depression and a 30% reduction in pain.

**Results:** 250 patients, with an average age of 55 years, participated in the study. Just over 50% were women and 60% were white. At 12 months, 37.4% of the intervention group were depression responders as opposed to 16.5% in usual care. Pain response was similar, with a 30% reduction seen in 41.5% of the treatment group as opposed to 17.3% of the controls. A composite response at 1 year was seen in 26% versus 7.9%. The number need to treat to achieve a composite response was 5.5.

**Conclusions:** Optimal antidepressant therapy combined with pain self-management can result in significant improvement in both depressive and pain symptoms over the course of 1 year.

**Reviewer's Comments:** Patients and primary care provider are often frustrated when treating both pain and depressive symptoms. Clearly, the response in patients receiving usual care was not great. This study was much more complicated than described here and required significant patient contact. But it does suggest that with careful attention to anti-depressant therapy and patient involvement in their own pain symptoms, both can improve significantly. (Reviewer-Deborah L. Greenberg, MD).

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Keywords: Musculoskeletal Pain, Depression, Coexistence

Print Tag: Refer to original journal article
A single CT of the abdomen and pelvis increases the lifetime risk of malignancy by an estimated 0.1%.

**Background:** 69 million CT scans were performed in the U.S. in 2007, and the radiation exposure from a single CT is substantial. The cancer risk of exposure to radiation doses of this magnitude has been estimated from epidemiologic studies of atomic bomb survivors.

**Objective:** To assess patient involvement in the decision to obtain a CT as well as their understanding of the risks of the radiation to which they would be exposed.

**Participants/Methods:** 768 consecutive adult patients waiting for an outpatient CT scan at the University of Michigan Hospital (2006 to 2007) were asked to complete a survey; 296 surveys were returned.

**Results:** The respondents were a highly educated group, with 85% reporting at least some college and 25% having a post-graduate degree. Approximately 83% of patients had discussed the reason for the CT with their doctor, and of these, almost all understood the reason for the study. When asked how much the radiation from an abdominal CT increased the risk of malignancy, only 2% chose the right answer (0.1%) on a multiple choice test, and the vast majority chose "don't know."

**Conclusions:** Few patients are aware of the risk of radiation exposure from a CT scan.

**Reviewer's Comments:** I found this brief article interesting primarily because I myself did not understand the magnitude of radiation exposure and risk associated with a CT scan. A previous study showed only 47% of radiologists and 9% of emergency department doctors actually knew that a CT scan increased the lifetime risk of cancer. Children are at higher risk than adults, both because they have more radiation sensitive tissue and because they have more years in which to develop a malignancy. The risk for any individual patient is obviously small, but on a population basis, it adds up. One of the references cited by this article (NEJM 2007; 357: 2277 to 2284) suggests that at current rates of CT usage, radiation from CT will be responsible for 1.5% to 2% of new cancer diagnoses in the United States. After reading this article, I will definitely think twice about indications for and alternatives to CT scanning, and will skip the screening studies for myself. (Reviewer-Karen A. McDonough, MD).

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Keywords: CT, Radiation Exposure, Malignancy

Print Tag: Refer to original journal article
Declining Adherence to Healthy Lifestyle Habits in U.S. Adults

King DE, Mainous AG III, et al:

Am J Med 2009; 122 (June): 528-534

Adherence to several commonly accepted healthy lifestyle habits have declined among U.S. adults between 1988 and 2006.

**Background:** A number of healthy lifestyle behaviors are associated with reductions in cardiovascular risk and overall mortality. Behaviors such as regular exercise, eating fruits and vegetables, not smoking, and maintaining healthy weight are widely understood to be healthful, yet it is not clear whether this professional and public knowledge translates into healthful behavior.

**Objective:** To evaluate any changes in adherence to healthy lifestyle habits during the past 2 decades.

**Methods:** The authors used the population-based National Health and Nutrition Examination Survey (NHANES) data set to examine healthy behaviors among U.S. adults (age range, 40 to 74 years). The following data elements were recorded from the NHANES database: body mass index (BMI); current smoking status; intake of fruits or vegetables; leisure time physical activity; and alcohol consumption. Study personnel measured height and weight, while the remainder of the data were self-reported. Healthy habits were defined as: BMI, 18.5 to 29.9; non-smoker; consumption of ≥5 fruits or vegetables daily, >12 episodes of leisure time physical activity per month, and moderate alcohol use (for women, ≤1 alcoholic beverages per day and for men, ≤2 drinks per day). The primary outcome was adherence to the 5 healthy habits compared between 2 time periods, 1988 to 1994 and 2001 to 2006.

**Results:** From 1988 to 1994 and 2001 to 2006, the percent of U.S. adults ages 40 to 74 years who are obese (BMI, 30) increased from 28% to 36% (P <0.05). Leisure time physical activity >12 times per month decreased from 53% to 43% (P <0.05); eating ≥5 fruits and vegetables decreased from 42% to 26% (P <0.05). Smoking rates have not changed appreciably (26.9% to 26.1%). Moderate alcohol use increased, 40% to 52% (P <0.05). Overall, adherence to all 5 healthy habits decreased from 15% to 8% (P <0.05). Declines in leisure time physical activity and fruit and vegetable consumption decreased more in men than women. Moderate alcohol intake has increased more in men than women.

**Conclusions:** Over the past 18 years, middle-aged U.S. adults, particularly men, are less compliant to recommended healthy habits.

**Reviewer’s Comments:** This study is consistent with the growing epidemic of obesity in this country. Along with a rising BMI, middle-aged adults are exercising less and eat fewer fruits and vegetables. These findings have important public health implications in future decades, as they may portend increasing the risks of cardiovascular disease, diabetes, and related disorders. It is unclear how our profession should respond to these largely secular trends, given how hard it is to change behavior. As an example, however, public health policies and expenditures have impacted smoking rates among U.S. adults over the past several decades; it may be that similar focused efforts can improve healthy lifestyle habits. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Healthy Lifestyle Habits, NHANES

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