Cancer Overdiagnosis Has Made Screening, Tx Choices More Complex

Overdiagnosis in Cancer.

Welch HG, Black WC:

J Natl Cancer Inst 2010; 102 (May 5): 605-613

Screening and imaging have led to the overdiagnosis of malignancy.

Background: Over the years, the diagnosis of "cancer" has increasingly come to mean less. At one time, it could simply be said to mean a neoplasm that, if left untreated, would generally result in the death of the patient. This had been mostly true when cancers were diagnosed that only came to attention because of clinical reasons. As improved technology has led to the detection of many cancers that are not associated with clinical manifestations, the diagnosis of cancer has come to mean less prognostically.
Objective: This article reviews the overdiagnosis of cancer. The authors describe overdiagnosis here as a condition that, if left untreated, would not lead to symptoms or death.
Results: Overdiagnosis with cancer happens when the cancers will either not progress (or even regress, such as with neuroblastoma) or when the patient dies of other causes prior to the cancer causing symptoms. Unfortunately, clinicians cannot know if a case represents an overdiagnosis unless the patient is not treated and dies from another cause prior to developing symptoms from their disease. From autopsy studies, it has been known that there is a considerable subclinical cancer disease reservoir. For example, from autopsy studies of men who died of other diseases, it is estimated that 30% to 70% of men >60 years of age have subclinical prostate cancer, that up to 36% to 100% of adults have papillary thyroid carcinomas, and that 7% to 39% of adult women have breast cancer. Disease reservoir by itself does not lead to overdetection. This generally happens because of screening, motivated by the fact that cancers detected at a lower stage tend to do better when treated. Mammography and prostate-specific antigen (PSA) testing are examples of screening tests that have led to overdiagnosis. Increased diagnostic imaging used for nonscreening purposes also frequently leads to detection of nonsymptomatic cancers. There is a great deal of evidence supporting the claims of overdiagnosis. Screening populations are diagnosed with more cancers than control populations, even with extremely prolonged follow-up periods. Examples include breast, prostate, and even lung cancer. The incidence rates of a number of cancers have drastically increased over the past 30 years, while little has changed with the mortality rates for those cancers. Examples here include breast, prostate, thyroid, kidney, and skin cancers. For example, the rate of diagnosis of thyroid cancer has more than doubled over the past 30 years, while mortality has not changed.
Conclusions: The overdiagnosis of cancer has made choices about screening and treatment more complex. Patients must be informed about the tradeoff for screening and treatment of their disease.
Reviewer's Comments: This article highlights problems with a purely histologic definition of cancer. Interestingly, in spite of this difficulty, diagnostic thresholds for some malignancies continue to decline. (Reviewer-Edward B. Stelow, MD).

Keywords: Cancer, Screening, Overdiagnosis, Thyroid, Breast, Prostate

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Numerous False Positives When Screening Smokers for Lung Ca With Low-Dose CT

Cumulative Incidence of False-Positive Test Results in Lung Cancer Screening: A Randomized Trial.

Croswell JM, Baker SG, et al:

Ann Intern Med 2010; 152 (April 20): 505-512

Using CT to screen smokers for lung cancer may cause 33% of patients to have a false-positive study after 2 years of screening.

Background: The use of CT to screen smokers for lung cancer is increasing despite a lack of good evidence on its benefits.
Objective: To determine the false-positive rate in patients being screened for lung cancer with low-dose chest CT.
Design: Randomized screening trial.
Methods: 3318 subjects were randomly assigned to either chest x-ray or low-dose CT scan, which was repeated 1 year later at the end of the study.
Results: False-positive results were more common with CT than with chest x-ray. In total, 31% of participants in the CT group and 14% in the chest x-ray group had at least 1 false-positive result compared with 2% true positives in the CT group and 1% in the chest x-ray group. The likelihood of a false-positive increased in those who had 2 screening studies, rising from a 21% false-positive rate after 1 study up to 33% after the second CT. Chest x-rays had a 9% false-positive rate after the initial study and a 15% rate after the second x-ray. In the entire cohort, there only 4 false-negative results, all in the chest x-ray group. Of everyone with at least 1 false-positive screening imaging study, 61% received ≥1 follow-up imaging tests. Seven percent of patients in the CT group and 4% in the chest x-ray group underwent some kind of invasive procedure, >50% of which were bronchoscopies. However, some patients went on to have more invasive procedures.
Conclusions: Risks for false-positive results on lung cancer screening tests are great after only 2 annual exams, especially for low-dose CT. Further study is necessary.
Reviewer's Comments: The results of this study are not surprising based on experience from clinical practice. Those of us ordering CT on smokers for other reasons have certainly come to appreciate the relatively high rate of incidental findings, many of which require additional imaging and a few that require invasive studies. With only 2 annual studies, it is unclear whether the false-positive rate will continue to rise with ongoing screening or will plateau over time, but the rise from 20% to 30% on second screening is not encouraging. This study certainly does emphasize our responsibility in counseling smokers considering screening for lung cancer that there is a relatively high rate of false-positive tests and a modest but nontrivial rate of invasive procedures needed for follow-up. Framed differently, for smokers who have an abnormal result over 2 years of screening, the odds are roughly 15:1 that the abnormality is benign. However, on the slim chance that the finding is malignant, it is important to pursue all such findings with appropriate diagnostic evaluation. (Reviewer-Christopher L. Knight, MD).

Keywords: Lung Cancer, False-Positive Tests, Smoking, Screening

Print Tag: Refer to original journal article

Dutasteride and Prostate Ca Prevention -- Results From the REDUCE Trial

Effect of Dutasteride on the Risk of Prostate Cancer.

Andriole GL, Bostwick DG, et al:

N Engl J Med 2010; 362 (April 1): 1192-1202

Prostate cancer prevention with 5α-reductase inhibitors is complex due to issues with detection bias. Benefits of short-term prevention may be offset by apparent increased risk for higher grade disease.

Objective: To evaluate whether dutasteride reduces the risk of incident biopsy-detected prostate cancer in men who are at increased risk for the disease.
Design: International multicenter randomized placebo-controlled double-blind parallel-group trial.
Participants/Methods: Men, from 50 to 75 years of age, with a prostate-specific antigen (PSA) level between 2.5 ng/mL and 10 ng/mL were included in the study. All had undergone a single prostate biopsy within 6 months prior to enrollment. Eligible patients were randomized to 0.5 mg/day dutasteride versus placebo over 4 years. Ultrasound was used to measure prostate volume at randomization and 2 and 4 years later. Biopsies were performed at enrollment and at 2 and 4 years per protocol and at any other time they were clinically indicated. The primary end point was biopsy-detected prostate cancer after 2 or 4 years of treatment.
Results: Overall, a 22.8% reduction in biopsy-detected prostate cancer was seen over 4 years in the dutasteride group compared to the placebo group. However, the risk of tumors with Gleason scores of 8 to 10 increased greatly in the dutasteride group during the final 2 years of the study.
Conclusions: Dutasteride therapy reduced the risk of biopsy-detected prostate cancer over 4 years, but raised concerns over increasing the risk of higher grade cancer.
Reviewer's Comments: In the April 1, 2010, edition of the *New England Journal of Medicine*, Andriole and colleagues from the REDUCE study group report their findings. The study was over a 4-year period, included men aged 50 to 75 years, and allowed PSA from 2.5 to 10 ng/mL. The men had entry biopsies, year 2 and year 4 biopsies, and were allowed "protocol-independent" for cause biopsies as well. In the "efficacy analysis", or "per-protocol" for the 4 years of the study, 659 of the 3305 men in the dutasteride group who had a biopsy (19.9%) and 858 of the 3424 men in the placebo group who had a biopsy (25.1%) received a diagnosis of prostate cancer, for an absolute risk reduction of 5.1%. An absolute reduction of 5% means that 1 out of every 20 men treated will get the prevention benefit. Of all the cancers diagnosed on biopsy, the higher grade (7 to 10) tumors were not significantly different for the 2 study groups. However, tumors of grades 8 to 10 were found at an alarming rate during the final 2 years of the study in the dutasteride group (12 high-grade tumors) compared to the placebo group (1 high-grade tumor). Putting this into perspective, this difference corresponded to a number needed to harm of 224 men. In other words, out of every 224 men taking dutasteride, 1 of them had an extra high-grade tumor found. Comparing this risk to the prevention benefit seen suggests that for every 224 men treated, 11 men will avoid a cancer diagnosis while 1 man will be diagnosed with a higher grade tumor. (Reviewer-Steven E. Canfield, MD).

Keywords: Prostate Cancer Prevention, Dutasteride

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Genetic Risk Factors for Breast Cancer -- Not Ready for Prime Time

Performance of Common Genetic Variants in Breast-Cancer Risk Models.

Wacholder S, Hartge P, et al:

N Engl J Med 2010; 362 (March 18): 986-993

Genetic risk factors for breast cancer have little benefit over clinical risk factors.

Background: Risk assessment for breast cancer continues to evolve. Breast screening programs use age as one risk factor, although age was recently the center of controversy for screening recommendations. Nongenetic factors have been used to assess risk, but as more genetic information regarding breast cancer becomes available, could genetic variants improve our risk assessment?
Objective: To determine if adding genetic information to nongenetic factors could improve our ability to predict which patients will develop breast cancer.
Design: Retrospective review of prospectively collected data from longitudinal studies including the Women's Health Initiative Observational Study and the Nurses' Health Study.
Participants: 11,588 patients were assessed. Of these, 5998 women did not develop breast cancer and 5590 women did.
Methods: Only patients who had complete genotype data were included. The nongenetic risk assessment used the Gail model, which was not adjusted for mammographic density or a diagnosis of atypical hyperplasia. Ten single nucleotide polymorphisms (SNPs) were assessed. The primary outcome was to model how well the various factors or combination of factors discriminated between patients with and without breast cancer. Receiver operator curves (ROC) were constructed and used to calculate the ability of the model to differentiate between these 2 populations.
Interventions: Numerous models were tested using the Gail model with and without SNP data. An ROC with an area under the curve (AUC) of 50% shows no discriminating ability, while an AUC of 100% would be perfect discrimination.
Results: Among the nongenetic factors, a history of a breast biopsy had the greatest AUC of 56%. All components of the Gail model had an AUC of 58%. All 10 SNPs had an AUC of 60%. When the Gail model and all 10 SNPs were combined, the AUC increased to 62%.
Conclusions: The addition of genetic factors added very little to a patient's risk assessment for breast cancer over more easily available clinical factors.
Reviewer's Comments: This paper starts with a discussion of personalized medicine. A genetic profile of an individual might help define the risk of disease before it occurs. Such information could be used to institute preventive measures, medical or surgical. The addition of 10 SNPs with a known association to breast cancer ranging from 22% to 87% did not enhance the ability to discriminate between women who developed breast cancer and those who did not. While there was a small increase, it is questionable if the increase could be justified when the nongenetic factors are available at minimal cost compared to the cost of the genetic profile. The idea is great, but our knowledge base may be inadequate. As we learn more about the genetics of cancer, new determinants may be found that would fulfill this promise of personalized medicine. (Reviewer-John A. Weigelt, MD).

Keywords: Genetic Risk Factors, Breast Cancer

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Multivitamins Taken Regularly May Increase Risk of Cancer

Multivitamin Use and Breast Cancer Incidence in a Prospective Cohort of Swedish Women.

Larsson SC, Åkesson A, et al:

Am J Clin Nutr 2010; 91 (May): 1268-1272

It may be time to question which, or if any, multivitamins should be recommended to patients.

Objective: To determine the impact of multivitamins and other dietary supplements on the risk of breast cancer in women.
Participants/Methods: A prospective study was done of 35,329 cancer-free women who completed a self-administrated 350-items questionnaire in 1997; the women were followed for 9.5 years. A total of 974 women were diagnosed with breast cancer during this time period.
Results: Multivitamin use was correlated with a statistically significant increased risk of breast cancer. The multivariate relative risk (RR) was 1.19, and this association did not differ significantly by hormone receptor status. The only other supplement that demonstrated a notable increased risk was zinc (RR=1.55), but this was not significant. In addition, multivitamin users were significantly more likely to take more individual supplements compared to those not taking multivitamins.
Conclusions: Multivitamin use may be associated with an increased risk of breast cancer.
Reviewer's Comments: What is going on here? The multivitamin is the best selling dietary supplement for men and women in the U.S., and has been for as long as I have been on this earth, but where is the evidence? We are waiting on a randomized major trial in the next year or 2 for Centrum®, but in the meantime, there is a suggestion of harm as much as a neutral or potential benefit with multivitamins. Some believe it is the zinc, others believe it is the folic acid because it is so easily utilized by cells, and others believe that there is no risk. However, I believe that when that oath said "first do no harm" that we were supposed to really follow it. Right? So, looks like I will only be recommending children's multivitamins for adults or nothing at all until someone can give me some idea or clue that these massive pills do something more than cost patients a bunch of money. (Reviewer-Mark A. Moyad, MD, MPH).

Keywords: Multivitamins, Breast Cancer Risk

Print Tag: Refer to original journal article

Use of Influenza Antiviral Therapy During Pregnancy Appears Safe

Maternal and Neonatal Outcomes After Antepartum Treatment of Influenza With Antiviral Medications.

Greer LG, Sheffield JS, et al:

Obstet Gynecol 2010; 110 (April): 711-716

Antiviral therapy for the treatment of seasonal influenza appears to be safe and is not associated with adverse perinatal outcomes.

Objective: To determine if there were any adverse maternal and/or neonatal outcomes in pregnancies with antenatal exposure to antiviral agents for the treatment of influenza.
Design: Retrospective study over a 4.5-year period.
Participants: 239 patients treated with antiviral agents for influenza.
Methods: Study encompassed 5 seasons of influenza. Patients that were febrile, had sustained tachycardia, threatened preterm labor, pneumonia, or were unable to tolerate oral therapy were admitted as inpatients and begun on antiviral therapy. Other patients were begun as outpatients. Antiviral medications used included amantadine, rimantadine, and oseltamivir. Since amantadine and rimantadine are the same class, patients receiving either of these two drugs were placed in the same group. There were 3 groups of patients evaluated: (1) those using M2 ion channel inhibitors, which were amantadine and rimantadine, (2) those using oseltamivir, and (3) a control group of patients not exposed to antiviral medications. Obstetric outcomes evaluated included preterm labor, premature rupture of membranes, development of gestational diabetes, development of preeclampsia, febrile episode in labor, and development of diabetes. Fetal outcomes included minor and major malformation, birth weight, rate of stillbirth, admission to neonatal intensive care unit (NICU), intraventricular hemorrhage, necrotizing enterocolitis, seizures, hyperbilirubinemia, duration of hospital stay, and neonatal death. Gestational age at time of exposure was also determined.
Results: 104 patients were in the M2 ion channel inhibitor group, 135 patients were in the oseltamivir group, and 82,097 patients in the control group. Of patients, 87% began therapy as inpatients and 13% as outpatients. Of patients, 13% began therapy in the first trimester, 32% in the second trimester, and 55% in the third trimester. There was no difference in either minor or major malformations between groups or a difference in the stillbirth rate. There was also no difference in the need for admission to the NICU, intraventricular hemorrhage, seizure, hyperbilirubinemia, or neonatal death. There was an increase in the rate of necrotizing enterocolitis in 2 infants exposed to an antiviral medication. Of these infants, 1 was exposed to amantadine in the second trimester; however, the mother was receiving a multi-drug antiviral regimen for HIV. This pregnancy was delivered at 32 weeks with fetal growth restriction. The second infant had been exposed to oseltamivir in the second trimester and was subsequently delivered at 29 weeks gestation.
Conclusions: There does not appear to be any adverse outcomes related to the use of antiviral therapy for influenza during pregnancy.
Reviewer's Comments: This study provides reassurance that antiviral therapy for the treatment of seasonal influenza is safe and not associated with adverse outcomes. The 2 infants having necrotizing enterocolitis were both delivered preterm and had other reasons for necrotizing enterocolitis, thereby making it less likely that necrotizing enterocolitis was related to medication exposure. (Reviewer-Thomas N. Tabb, MD).

Keywords: Maternal & Neonatal Outcomes, Antepartum Treatment, Influenza, Antiviral Medications

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Infants With New-Onset Afebrile Seizures -- Consider CT or MRI

New-Onset Afebrile Seizures in Infants: Role of Neuroimaging.

Hsieh DT, Chang T, et al:

Neurology 2010; 74 (January 12): 150-156

Because of a high likelihood of intracranial abnormalities in infants aged <2 years with new-onset afebrile seizures, some type of neuroimaging (CT or MRI) should be obtained.

Background: In a child who has a seizure not associated with a fever, there has been controversy as to which diagnostic modalities, if any, should be used to evaluate for a possible underlying problem.
Objective: To investigate presenting characteristics of new-onset afebrile seizures in younger children and the yield of neuroimaging.
Design/Participants: Prospective data were obtained on 317 patients between 1 and 24 months of age who presented with new-onset afebrile seizures at the Children's National Medical Center.
Methods: As part of a protocol, patients underwent basic laboratory studies as well as imaging with a head CT. MRIs were performed if there continued to be focal findings or the CT was abnormal or equivocal. Seizures were classified, and the witnessed duration of seizures and the total number of seizures were noted.
Results: EEG studies were performed on 90%, CT on 94%, and MRI on 57%. Most seizures were classified as tonic-clonic, with the second most common type in patients aged <1 year being infantile spasms. Recurrence was common. Most patients had >1 seizure on presentation and these seizures were typically brief in nature. In 44% of patients, seizures lasted <1 minute; in 8%, they lasted >20 minutes. One third of CT studies were abnormal; in 9% of patients, the CT required acute medical or surgical management, such as treatment for diffuse edema, acute hydrocephalus, vascular malformation, stroke, trauma, or tumor. Of the MRIs, more than one-half were abnormal. The most common abnormality was cerebral dysgenesis in 16%. In patients whose CT was originally normal, MRIs were obtained in about one-third. However, only 1 MRI study resulted in altered medical management.
Conclusions: New-onset seizures in afebrile infants aged <24 months are usually brief. Recurrence is common, and strong consideration should be given to admitting patients in younger age ranges. In addition, a CT scan can alter management significantly in nearly 1 of 10 infants. MRI should be strongly considered for all infants in these settings, as nearly 1 of 6 has cerebral dysgenesis.
Reviewer's Comments: There has been debate about the value of early imaging in infants with afebrile seizures. This paper demonstrates a high yield in these younger patients when early imaging is performed. The radiation risk of CT appears to be outweighed by the likelihood of detecting an important abnormality. In these patients, 9% of those who underwent CT required acute intervention. The value of the MRI is more debatable. MRI did pick up abnormal findings in more than one-half of infants, although it did not alter management except in a single case. However, identifying cerebral dysgenesis and possible etiologies can potentially make a significant difference in terms of counseling and prognosis, which are vital for parents. (Reviewer-Mark F. Ditmar, MD).

Keywords: Afebrile Seizures, Infants, Neuro-Imaging

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Do Fibrates Add to Statin Therapy in High-Risk Diabetics?

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus.

The ACCORD Study Group:

N Engl J Med 2010; 362 (April 29): 1563-1574

In patients with high-risk type 2 diabetes, the addition of a fibrate to statin therapy does not improve cardiovascular outcomes.

Background: The role of adding fibrate therapy to statins for more aggressive management in diabetic patients is not clear. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study sought to examine the impact of various interventions on cardiovascular outcomes in patients with diabetes mellitus.
Objective: To determine whether the combination of statin and fibrate therapy would improve cardiovascular outcomes as compared to statin alone in high-risk diabetics.
Design/Methods: The ACCORD Lipid trial looked at a subset of patients enrolled in the larger ACCORD trial. To be eligible for this arm, participants had to have low-density lipoprotein cholesterol (LDL-C) of 60 to 180 mg/dL; high-density lipoprotein cholesterol (HDL-C) <55 mg/dL for women and blacks; or <50 mg/dL for others. Participants also needed to have triglycerides <750 mg/dL for those not on lipid-lowering treatment and <400 mg/dL for those on treatment. All patients were placed on simvastatin 20 mg daily (later titrated to maximum of 40 mg). Patients were then randomized to either fenofibrate 160 mg or placebo daily (with dose adjusted based on glomerular filtration rate). Lipids and muscle and liver enzymes were followed regularly. A composite of major cardiovascular events was the primary outcome (nonfatal stroke or myocardial infarction or cardiovascular death).
Results: 5518 patients were enrolled with an average age of 62 years; 31% were women. At entry, roughly two thirds were on lipid-lowering medication. After an average of 4.7 years, LDL-C had decreased from around 100 mg/dL to approximately 80 mg/dL in both groups. Comparing the fenofibrate to placebo groups, HDL increased and triglycerides decreased in both groups. However, fenofibrate led to a greater increase in HDL (3.2 mg/dL vs 2.3 mg/dL) and a greater drop in triglycerides (42 mg/dL vs 16 mg/dL). As for the primary outcome, there was no significant difference in major cardiovascular events or overall mortality. Of note, in a subgroup analysis, those patients in the lowest one third of HDL-C and highest one third of triglycerides did show a modest benefit with fenofibrate (12.4 vs 17.4%). There were no differences in rates of significant creatinine kinase levels.
Conclusions: In patients with high-risk type 2 diabetes, the addition of a fibrate to statin therapy does not improve cardiovascular outcomes.
Reviewer's Comments: The ACCORD trial attempted to answer a number of clinical questions. Unfortunately, by doing so, it put significant constraints on the lipid arm. First, the entry criteria were broad, decreasing the likelihood of finding differences (including that most patients were on lipid-lowering treatment at baseline). However, it is reasonable to state that fibrates probably do not add much to the average treated diabetic. Whether there is a subgroup that would benefit (such as those with low HDL and high triglycerides) has not been definitively determined. (Reviewer-Mark E. Pasanen, MD).

Keywords: Diabetes Mellitus, Statins, Fibrates, Cardiovascular Disease

Print Tag: Refer to original journal article

An Antibiotic to Avoid in Your Warfarin Patients

Hemorrhage During Warfarin Therapy Associated With Cotrimoxazole and Other Urinary Tract Anti-Infective Agents: A Population-Based Study.

Fischer HD, Juurlink DN, et al:

Arch Intern Med 2010; 170 (April 12): 617-621

Cotrimoxazole significantly increases the risk of gastrointestinal bleeding in older anticoagulated patients.

Background: Warfarin is a perennial leader in adverse drug events reported to the federal government. Excessive anticoagulation and bleeding are often precipitated by a drug-drug interaction. Antibiotic treatment of acute infections can be particularly problematic, as many antibiotics disrupt the normal gut flora and endogenous vitamin K production. Some, including cotrimoxazole, also inhibit the cytochrome P450 isoenzyme responsible for metabolizing warfarin.
Objective: Most of us recognize that co-treatment with warfarin and cotrimoxazole can increase the international normalized ratio (INR), but how much bleeding does the combination actually cause and how does that compare with other antibiotics?
Design: Population-based case-control study.
Participants: Chronically anticoagulated Ontario residents aged ≥65 years.
Methods: The authors reviewed a set of provincial health care databases to identify a large (134,000) cohort of chronically anticoagulated patients. Of these, 2151 were found to have been hospitalized for upper gastrointestinal bleeding. Each of these case patients was matched with 10 age- and sex-matched controls from the anticoagulated group. They then examined drug records of cases and controls, looking for exposure to cotrimoxazole and other drugs commonly used to treat urinary tract infection within 14 days prior to hospitalization. The other drugs included amoxicillin, ampicillin, ciprofloxacin, norfloxacin, and nitrofurantoin.
Results: During the study period, 34% of all warfarin patients received at least 1 prescription for an antibiotic. After adjusting for prior upper gastrointestinal bleed, comorbid illness, and concomitant drug use, the authors found that case patients were much more likely to have received cotrimoxazole in the preceding 14 days (OR, 3.84). Treatment with ciprofloxacin increased risk to a lesser extent (OR, 1.94). There was no significant association seen between exposure to the other antibiotics studied and admission for upper gastrointestinal bleed, including norfloxacin.
Conclusions: Cotrimoxazole significantly increases the risk of gastrointestinal bleeding in older, anticoagulated patients. Alternative antibiotics should be used when at all possible.
Reviewer's Comments: I do not use a lot of norfloxacin, but I may think of it the next time I need to treat a urinary tract infection in a warfarin-treated patient. Ciprofloxacin is a better choice than cotrimoxazole, but does still appear to increase the risk of hospitalization for gastrointestinal bleeding. (Reviewer-Karen A. McDonough, MD).

Keywords: Warfarin, Hemorrhage, Cotrimoxazole

Print Tag: Refer to original journal article

Is Tight Blood Pressure Control in Diabetes Important?

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus.

The ACCORD Study Group:

N Engl J Med 2010; 362 (April 29): 1575-1585

In high-risk patients with diabetes, intensive BP management does not decrease the rate of important cardiovascular outcomes.

Background: Current guidelines from the American Diabetes Association recommend target blood pressure (BP) of <130/80 mm Hg in patients with diabetes mellitus, although there are limited data supporting this goal. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a large trial that previously reported outcomes on glycemic control.
Objective: To evaluate the effect of intensive BP control on cardiovascular outcomes in high-risk diabetic patients.
Design: In the ACCORD trial, all patients were randomized to either intensive or standard glycemic control. In addition, patients were assigned to either an intensive blood pressure arm or an intensive lipid-lowering arm.
Participants: Patients aged ≥40 years with type 2 diabetes mellitus, glycated hemoglobin ≥7.5%, and known cardiovascular disease were eligible. In addition, patients aged ≥55 years with evidence of atherosclerosis, left ventricular hypertrophy, albuminuria, or at least 2 additional risk factors were eligible. For the blood pressure arm, participants had to be on ≤3 BP medications with a systolic BP between 130 and 180 mm Hg.
Methods: Patients were randomized to a systolic BP goal of either 120 or 140 mm Hg. The trial was not blinded and did not dictate an algorithm for blood pressure medication (although physicians were required to include drug classes with evidence for benefit in diabetics). The primary outcome was the first occurrence of the composite of major cardiovascular event (nonfatal myocardial infarction or stroke or cardiovascular death).
Results: 4733 patients were enrolled in ACCORD BP trial, with an average age of 62 years and average blood pressure of 139/76. In total, 48% were women. After a mean follow-up of 4.7 years, BP in the intensive group was lower than the regular-care group (119/64 vs 134/71 mm Hg). There was no significant difference in major cardiovascular events (1.87%/year in the intensive group vs 2.09%/year in the regular-care group). There was no significant difference in overall mortality. There was a slightly lower stroke rate in the intensive group (0.32%/year vs 0.53%/year). The number needed to treat for intensive BP control for 4.7 years to prevent 1 stroke was approximately 90.
Conclusions: In high-risk patients with diabetes, intensive BP management does not decrease the rate of important cardiovascular outcomes.
Reviewer's Comments: This study sheds some doubt on the standard to lower BP <130 mm Hg in diabetics. However, one potential limitation noted by the authors was the low overall event rates, perhaps because many higher-risk patients were enrolled in the lipid portion. As well, even the regular-care group had relatively well-controlled blood pressure. However, from this trial, it appears that aggressively managing systolic BP from the mid-130's down to <120 mm Hg does not confer a major benefit. (Reviewer-Mark E. Pasanen, MD).

Keywords: Hypertension, Type II Diabetes Mellitus, Cardiovascular Outcomes

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High BP Variability Predicts Poor Outcomes

Prognostic Significance of Visit-to-Visit Variability, Maximum Systolic Blood Pressure, and Episodic Hypertension.

Rothwell PM, Howard SC, et al:

Lancet 2010; 375 (March 13): 895-905

Patients with high visit-to-visit variability in BP have more strokes and coronary events.

Background: Variability in blood pressure (BP) is associated with higher rates of cardiovascular (CV) events, but no good studies exist looking at variability between clinic visits.
Objective: To determine if there is an association between visit-to-visit BP variability and CV events.
Design: Retrospective analysis of randomized trial data.
Participants: Approximately 25,000 patients enrolled in a variety of trials monitoring blood pressure and cardiovascular events.
Methods: Data were analyzed to determine the risk of stroke in relation to visit-to-visit variability in BP and maximum blood pressure in patients with previous transient ischemic attack and in patients with treated hypertension.
Results: As expected, risk of stroke went up with increasing mean systolic BP. However, risk also went up as variability in systolic BP increased. Patients whose BP was consistently near 140 had a lower risk of stroke than those whose BP varied between 120 and 160 on clinic visits. When the authors stratified the groups into 10 deciles of variability, from lowest to highest, the hazard ratio for stroke or coronary events was 3 to 4 times higher in the decile with the greatest variability than the one with the least. Interestingly, visit-to-visit variability was more predictive of ischemic than hemorrhagic stroke, and remained predictive whether or not patients had had a prior stroke.
Conclusions: Visit-to-visit variability in systolic BP and maximum systolic BP are strong predictors of stroke, independent of mean systolic BP. Increased residual variability in systolic BP in patients with treated hypertension is associated with a high risk of vascular events.
Reviewer's Comments: This is a very interesting study that could be important for clinical practice. An accompanying editorial points out that the observation that variability is associated with risk is not new, and has been examined in the literature for almost 20 years. However, most prior trials looked at short-term variability BP using either home BP readings or ambulatory monitoring, not at the more readily available BPs taken during clinic visits. Admittedly, these were antihypertensive trials, so the BPs during clinic visits were taken with particular care and usually multiple times in order to minimize white coat effect. However, I think that it still sends an important message to those of us who manage hypertension: patients with BPs all over the map on subsequent clinic visits are at higher risk of stroke and coronary events than patients whose BPs are stable, even if the BPs average out to the same value. We should be paying close attention when patients have BPs that vary widely between visits, especially if they have a prior stroke. (Reviewer-Christopher L. Knight, MD).

Keywords: Hypertension, Blood Pressure, Cardiovascular Events

Print Tag: Refer to original journal article

Is There a Preferred Repair for Abdominal Aortic Aneurysm?

Endovascular Versus Open Repair of Abdominal Aortic Aneurysm.

The United Kingdom EVAR Trial Investigators:

N Engl J Med 2010; 362 (May 20): 1863-1871

There appears to be no significant benefit with endovascular repair over surgical repair of abdominal aortic aneurysm.

Background: With an increasingly aging population, abdominal aortic aneurysm (AAA) is becoming more common especially in older men. With the risk of rupture increasing with size, repair is recommended -- frequently endovascular or open surgical repair. Prior studies have shown benefit with endovascular repair as compared to open surgical repair for 30-day mortality. Follow-up was short in these studies. The EndoVascular Repair 1 trial (EVAR1) was designed to compare long-term outcomes of endovascular repair versus open repair of large AAAs.
Design: Large randomized trial.
Participants: 1252 patients with AAA.
Methods: Patients aged >60 years with an AAA >5.5 cm in diameter by CT were recruited for the EVAR1 trial if they fit anatomic and clinical criteria for surgical and endovascular repair. These patients were randomized to either open surgical or endovascular repair. They were followed up with CTs at 1 and 3 months and annually thereafter. Primary end point was all-cause mortality.
Results: There were no significant differences between groups at baseline. Mean age was 74.1±6.1 years and 90% were men. Mean diameter of AAA was 6.4±0.9 cm. All patients were followed until September 2009. Median follow-up until death or end of study was 6 years. The 30-day mortality was 1.8% in the endovascular group and 4.3% in the open surgical repair group. Of patients, 2.3% in the endovascular repair and 6% in the open surgical repair group died during hospitalization for the repair. At study end, there was no significant difference in the total mortality (7.5 and 7.7 deaths per 100 person years in the endovascular repair group and open surgical repair group, respectively). Graft-related complications and re-interventions were 3 to 4 times more common in the endovascular group. Endovascular repair was $8000 more costly than open surgical repair for the primary repair and cost $5000 more in 8 years of follow-up.
Conclusions: Endovascular repair was associated with lower operative mortality, but there was no significant difference in total mortality or aneurysm-related mortality in the long term when compared to open surgical repair. Moreover, graft-related complications and re-interventions were more common and more costly in the endovascular group.
Reviewer's Comments: This trial shows that even though initial procedural mortality is much lower in the endovascular group, the benefit is lost in the long term due to increased graft-related complications and aneurysm related mortality. With this current evidence, a patient with AAA, if they fit criteria for surgical therapy, would benefit in the long term more from surgical repair than with endovascular repair and would be cheaper. (Reviewer-Pradeep S. Arumugham, MD).

Keywords: Abdominal Aortic Aneurysms, Treatment

Print Tag: Refer to original journal article

Don't Watch and Wait When Aortic Stenosis Is Very Severe

Early Surgery Versus Conventional Treatment in Asymptomatic Very Severe Aortic Stenosis.

Kang DH, Park SJ, et al:

Circulation 2010; 121 (April 6): 1502-1509

Early aortic valve surgery improves long-term survival in asymptomatic patients with very severe aortic stenosis.

Background: Management of asymptomatic aortic stenosis (AS) remains controversial. Sudden death occurs in approximately 1% of patients per year. However, surgery has attendant risks of morbidity and mortality, though less in recent years due to improved techniques.
Design: Prospective study.
Participants: 197 consecutive asymptomatic patients with “very severe” AS.
Methods: A prospective registry was set up in 1996 and later queried for patients with "very severe" asymptomatic AS defined as aortic valve area ≤0.75 cm2 and either peak aortic velocity ≥4.5 m/sec or mean aortic valve gradient ≥50 mm Hg on Doppler examination. Patients were excluded because of dyspnea, syncope, angina, ejection fraction (EF) <50%, moderate or severe aortic regurgitation, significant mitral disease, malignancy, and age >85 years. Pre-existing coronary disease was also an exclusion, though 6 patients with incidentally discovered coronary artery disease (at preoperative angiography) were included. Early surgery or conventional treatment was at the discretion of the treating physician.
Results: 102 patients had early surgery with no operative mortality; 95 had conventional treatment. During follow-up there were no cardiac and 3 non-cardiac deaths in the surgical group, as compared with 18 cardiac and 10 non-cardiac deaths in the conventional group. Estimated 6-year survival and cardiac mortality-free survival were 98% and 100% in the surgical group versus 68% and 76% in the conventional group (P <0.001). Of sudden death cases, 7 were asymptomatic at the last exam, as were 7 cases of heart failure death. Additionally, 57 propensity score-matched pairs were examined, with similar results; estimated 6-year survival and cardiac mortality-free survival were 96% and 100% in the surgical group versus 65% and 74% in the conventional group. Of patients in the conventional group, 46 underwent late surgery; they had significantly more left ventricular dysfunction in the immediate postoperative period than did the early surgery group.
Conclusions: In this study, early aortic valve surgery improved long-term survival in asymptomatic patients with very severe AS. Further, >80% of survivors in the conventionally-treated group eventually came to surgery.
Reviewer's Comments: This research strongly supports early valve replacement in asymptomatic patients with very severe AS. This is in line with other work showing high event rates and risk of rapid deterioration in this population. One problem in caring for such patients is in knowing that they are truly asymptomatic. Many are sedentary and others probably dismiss mild symptoms as due to other causes. Given the very low surgical mortality with current techniques, it just makes sense to operate early when AS is "very severe." Several other points of interest: half of all patients had bicuspid valves, confirming other work; degree of calcification correlated with mortality in the conventional group; though the group as a whole showed hemodynamic progression, there was much inter-individual variation. Interestingly, survival varied significantly according to gender with women showing better survival than men, a finding left unexplained. (Reviewer-Gregg S. Pressman, MD).

Keywords: Severe Aortic Stenosis, Early Surgery, Conventional Therapy

Print Tag: Refer to original journal article

Should We Recommend Circumcision for Long-Term Benefits?

Male Circumcision for the Prevention of Acquisition and Transmission of Sexually Transmitted Infections: The Case for Neonatal Circumcision.

Tobian AAR, Gray RH, Quinn TC:

Arch Pediatr Adolesc Med 2010; 164 (January): 78-84

Numerous recent randomized trials have demonstrated significant benefits of circumcision for the prevention of acquisition and transmission of STIs prompting calls for its routine use for newborn males.

Background: As recently as 2005, the American Academy of Pediatrics (AAP) stated that there is not enough existing scientific evidence for medical benefits to recommend routine neonatal circumcision.
Objective: To review recent studies regarding the effect of circumcision as prevention for sexually transmitted infections (STIs).
Design: Review article from a group of physicians from Johns Hopkins University.
Results: The authors argue that since that 2005 AAP recommendation, there have been multiple randomized trials that have evaluated male circumcision for prevention of STIs, and these warrant a look from the AAP. Regarding the transmission of human immunodeficiency virus, 3 large randomized controlled trials of >10,000 men conducted in South Africa, Kenya, and Uganda found that circumcision in heterosexual males reduced the HIV acquisition by 50% to 60% compared to those who were not circumcised. Based on these data, the World Health Organization recommended circumcision as a preventative measure to reduce HIV acquisition. Of note, whether circumcision can definitively reduce HIV acquisition among men who have sex with men is less certain. Regarding herpes simplex type 2 infections, 2 randomized trials published in 2009 found that male circumcision decreased HSV-2 acquisition by 28% to 34%. The data on bacterial STIs, such as gonorrhea, are equivocal. For syphilis, 1 meta-analysis estimated a decreased risk of approximately one-third. Other studies have found slight decreases in *Trichomonas vaginalis* and *Chlamydia trachomatis* among circumcised males. However, among female partners of circumcised men, bacterial vaginosis was reduced by 40% and *Trichomonas* by 48%. For human papillomavirus, randomized trials are also very impressive, with circumcision resulting in decreases in HPV prevalence by 32% to 35% in men. These preventive factors are counterbalanced by the risks of circumcision with a generally accepted rate of 0.2% to 0.6%, most commonly bleeding and local infection. Other more sinister complications, such as meatal stenosis, are extremely rare.
Conclusions: New information on the long-term benefits of circumcision in preventing STIs should prompt the AAP to revise their policy on circumcision.
Reviewer's Comments: The authors note that the AAP's blessing is not just window dressing. Medicaid coverage does not cover the cost of male circumcision in 16 states, potentially disproportionately affecting disadvantaged minorities who, as adults, have the highest risk of HIV and STIs. If the AAP says the procedure is indicated, Medicaid coverage would hopefully increase. (Reviewer-Mark F. Ditmar, MD).

Keywords: Prevention, Transmission, Circumcision

Print Tag: Refer to original journal article

SSRIs for Stroke?

Escitalopram and Enhancement of Cognitive Recovery Following Stroke.

Jorge RE, Acion L, et al:

Arch Gen Psychiatry 2010; 67 (February): 187-196

Escitalopram may improve verbal and visual memory functions in patients who suffer stroke.

Background/Objectives: There is interest in restorative therapies that might be affective within the first critical months after a stroke when any reversible improvement in function most likely occurs and that act on widely distributed aminergic and cholinergic systems. Antidepressants are known to exert their effects via increased expression of neurotrophic factors, neural and glial cell precursors, and axonal and synaptic development. Serotonin specifically is involved in neuroplastic and neurogenic processes. It would seem possible then, that selective serotonin reuptake inhibitors (SSRIs) might have some restorative impact on injured or vulnerable neural systems.
Methods: Eligible patients admitted and evaluated at the University of Iowa Stroke Center, excluding those with a *DSM-IV* defined depressive disorder, a Hamilton Anxiety Rate Scale (HAM-D) score >11, or with severe communicative deficits or medical problems, were randomized to escitalopram, placebo, or a standardized form of problem-solving therapy (PST). Patients were evaluated at baseline and at 3, 6, 9, and 12 months with *DSM-IV* structured diagnostic interviews and symptoms scales, neuropsychological testing including the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), as well as the Functional Independence Measure (FIM).
Results: 129 patients were randomized within 3 months of stroke onset. Controlling for HAM-D scores, patients with escitalopram showed significantly greater improvement in overall RBANS score (9.9 change in score vs 1.9 for PST group and 4.0 for placebo). Escitalopram showed more specific significantly greater impact on improvement in verbal and visual delayed and immediate memory and FIM scores but not in attention, language, or visuospatial domains.
Conclusions: Independent of any effects on depression and mood, escitalopram appears to have effects on memory improvement in patients recovering from stroke, and this effect also appears to improve rated functional performance.
Reviewer's Comments: The long-term neurocellular effects that are still unclearly defined in terms of their mechanism of action on mood may be proving to have larger neuroprotective and therapeutic applications. Expect, then, increasing attention to the development of more focused and varied serotonin system-acting pharmacology, which may also impact the care of mood disorders. (Reviewer-Gary S. Belkin, MD, PhD, MPH).

Keywords: Escitalopram, Stroke

Print Tag: Refer to original journal article

Is Alcohol Good for Your Heart?

Alcohol Intake and Risk of Coronary Heart Disease in Younger, Middle-Aged, and Older Adults.

Hvidtfeldt UA, Tolstrup JS, et al:

Circulation 2010; 121 (April 13): 1589-1597

Light to moderate alcohol consumption is beneficial in decreasing the incidence of CHD, including in younger adults.

Background: Alcohol consumption has been demonstrated to be associated with a lower risk of coronary heart disease (CHD). It is not clear whether the benefit of alcohol extends to younger adults, as the risk of CHD is low in men aged <40 years and women aged <50 years. Accordingly, most studies have relatively few younger adults; therefore, conclusions are not readily drawn about the benefit of alcohol in these age groups. The cause of CHD in younger adults is often different than in older adults, with the former more often reflecting genetic traits, thus they may not have the same benefit of alcohol consumption.
Objective: To examine whether the beneficial effect of alcohol on coronary heart disease depends on age.
Design: Pooled data from prospective studies of a minimum of 150 incident cases of CHD and appropriate and validated assessment of dietary intake.
Methods: Of 12 studies willing to share data, 1 was excluded because it only evaluated nondrinkers, 2 because of incomplete alcohol data, and 1 because CHD information was self-reported. Thus, 8 studies were evaluated, including average daily alcohol intake. Incident CHD was the primary outcome. Cox proportional hazards regression models were performed.
Results: The pooled population was just over 199,000 women and over 79,000 men with approximately 1.4 million and approximately 600,000 person-years of follow-up, respectively. Heavier alcohol intake was associated with more smokers, physically inactive subjects, lower education levels, hypertension, and lower intake of fiber. Subjects were analyzed by age <50 years, 50 to 59 years, and >60 years. The incidence rates of CHD were lowest in the youngest age group. The incidence of CHD was lower in all age groups and in both genders for those with low to moderate alcohol intake when compared with abstainers. The pattern of consumption of alcohol was not assessed.
Conclusions: Alcohol in moderate amounts protects against CHD, regardless of age. However, because younger adults are at a low risk of CHD, recommendations regarding alcohol consumption must take into account all-cause mortality, such as that contributed by accidents and cancer.
Reviewer's Comments: Yet another piece of the alcohol and CHD puzzle, this study suggests that there is in fact a benefit of alcohol in younger adults, but importantly identifies that the benefit may be negligible if taken in the context of total mortality, where the negative aspects of alcohol consumption such as accidents and cancer, may offset the CHD benefit. This is a very large study, with the usual flaws in all such studies associated with dietary questionnaires. Nonetheless, it is one of the first large studies to be able to provide reasonable data on younger adults. It does not address the potential that binge drinking, likely more common in younger adults, would have a different impact on CHD incidence. (Reviewer-Karen Stout, MD).

Keywords: Alcohol, Coronary Heart Disease, Prevention

Print Tag: Refer to original journal article

Does Chronic Oral Anticoagulation Reduce Mortality Risk After MI?

Long-Term Effect of Chronic Oral Anticoagulation With Warfarin After Acute Myocardial Infarction.

Haq SA, Heitner JF, et al:

Am J Med 2010; 123 (March): 250-258

Chronic oral anticoagulation does not reduce mortality post-myocardial infarction.

Background: Single or dual antiplatelet therapy is the currently-practiced antithrombotic regimen status-post acute myocardial infarction (MI). Usage of additional chronic oral anticoagulation (OAC) is often patient, institution, or cardiologist specific, as it remains unclear whether additional OAC improves patient outcomes.
Objective: To assess the risk and benefit of long-term OAC status-post recent MI.
Design: Meta-analysis of 10 randomized clinical trials.
Methods: Data were analyzed comparing warfarin-containing OAC regimens with or without aspirin with non-OAC regimens with or without aspirin for patients with recent myocardial infarction. Primary end point was defined as all-cause mortality, but other end points were also individually examined. These included recurrent infarction, stroke, and major bleeding. Odds ratio (OR) (fixed effect, OR <1 indicates benefit for OAC) for death and other ischemic and hemorrhagic complications at the longest interval of follow-up available was then calculated.
Results: There were 24,542 patients included in the pooled data, of which 14,062 were assigned to OAC and 10,480 to no OAC. Patients were followed for 3 to 63 months, and reperfusion therapy was administered to 6009 patients (25%). Death occurred in 2424 patients (9.9%), comprised of 1279 patients in the OAC group and 1145 in the no-OAC group (OR 0.97; 95% CI, 0.88 to 1.05; *P* =0.43). There were 2430 new infarctions (9.9%) with no significant difference between groups (*P* =0.18). There was also significantly more major bleeding in the OAC group (*P* <0.001). However, stroke occurred in 578 patients (2.4%), 271 in the OAC group and 307 in the no OAC group (*P* =0.001). A subset of patients (n=11,920) randomized to aspirin versus aspirin and OAC underwent separate analyses, with the results being very similar.
Conclusions: Among approximately 25,000 patients with recent MIs meta-analyzed, OAC with or without aspirin did not reduce mortality or reinfarction, as compared with placebo or aspirin. There is reduction in stroke, but there is an association with significantly more major bleeding.
Reviewer's Comments: In this meta-analysis in approximately 25,000 patients for nearly 90,000 patient years, oral anticoagulation was found to not reduce all-cause death or re-infarction. Epidemiological data supports the association of a potential benefit in reducing factor VII levels to reduce the risk of vascular thrombotic events. Low-dose warfarin appears reasonable. However, in this meta-analysis, the INR ranged from 1.5 to 4, and no benefit was seen. A possible explanation is that rupture of a stable plaque results in platelet activation and aggregation, and warfarin has a limited role in preventing this type of a thrombotic cascade. A potential study limitation is that patient subsets, such as those with large anterior wall myocardial infarctions and left ventricular thrombus, could not be adequately assessed for possible benefits of oral anticoagulation therapy. (Reviewer-Suraj Maraj, MD).

Keywords: Chronic Oral Anticoagulation, Warfarin, Acute Myocardial Infarction, Long-Term Effect

Print Tag: Refer to original journal article

Do Bisphosphonates Reduce Mortality in Osteoporosis Patients?

Effect of Osteoporosis Treatment on Mortality: A Meta-Analysis.

Bolland MJ, Grey AB, et al:

J Clin Endocrinol Metab 2010; 95 (March): 1174-1181

Treatment for osteoporosis reduces vertebral and non-vertebral fracture risks, and does indeed reduce mortality in older, frailer individuals.

Objective: To determine if osteoporosis treatment reduces mortality.
Design: Meta-analysis.
Methods: Study utilized data derived from MEDLINE publications and Cochrane trials as well as conference abstracts from the American Society for Bone and Mineral Research. Eligible studies included randomized, placebo controlled trials of approved anti-osteoporosis medications in a population >50 years, and of sufficient size and duration to be valid. Trials of estrogen and SERMs were specifically excluded. Of 5200 studies surveyed, 10 were eligible for inclusion based on the author's criteria.
Results: The 10 studies included 1,417 deaths in 39,549 participants, who were on 1 of 4 agents: (1) risedronate, (2) strontium ranelate, (3) zoledronic acid, or (4) denosumab. Osteoporosis treatment was associated with an 11% reduction in overall mortality, and this reduction was greatest in trials utilizing populations with higher mortality rates (ie, in more frail populations).
Conclusions: Treatment for osteoporosis reduces vertebral and non-vertebral fracture risks, and does indeed reduce mortality in older, frailer individuals.
Reviewer's Comments: This was a good study showing that not only does osteoporosis treatment reduce subsequent incidence of fracture, it also reduces mortality. As the authors point out, only a portion of post-fracture mortality is related to the fracture itself. So, other factors must contribute to the lowered mortality as a result of osteoporosis treatment. Could it possibly be a statin-like effect of bisphosphonates? Obviously, prevention of future fracture contributes to diminished mortality in osteoporotic individuals who are treated, but there are other unknown factors contributing to this reduced mortality as a consequence of osteoporosis pharmacotherapy. (Reviewer-Berel Held, MD).

Keywords: Osteoporosis, Treatment, Mortality

Print Tag: Refer to original journal article

One Solution to Malpractice Problem -- Change the Evidence Standard

Solving the Medical Malpractice Crisis: Use a Clear and Convincing Evidence Standard.

Engel E, Livingston EH:

Arch Surg 2010; 145 (March): 296-300

A change of the evidence standard from "more likely than not" to "clear and convincing" might sharply reduce malpractice judgments against physicians.

Objective: To propose a change in the evidence standard upon which malpractice judgments are based.
Design: A review article on the current evidence standard for malpractice awards with recommendations on change.
Results: Rather than the current tort reform proposals that rely mainly on damage control after a malpractice verdict is rendered, the authors believe attention should be directed to the courtroom process before decisions are made. Evidence standards vary in courtroom settings. In criminal cases, the most rigid standard -- beyond a reasonable doubt -- is applied. An intermediate standard -- clear and convincing -- is applied for custody decisions and medical board actions. The most liberal standard is "preponderance of the evidence," which equates to "more likely than not," meaning any probability >50% that actions are improper. It is this standard that is applied in medical malpractice cases. The authors argue that changing the standard from the "more likely than not" to "clear and convincing" would solve most malpractice problems for physicians in a way that they believe would be palatable to the public and the legal community. There can be a high false-positive rate with a physician who is innocent potentially having only a 50/50 chance of being found not guilty in a trial. Clear and convincing equates to a 95% probability standard, while beyond a reasonable doubt equates to 99%. Studies have found an overall incidence of 0.8% to 1% of true negligence in hospital admissions. At these prevalence rates, if there are 1000 cases, 10 would constitute true malpractice, with 990 cases in which no malpractice was committed. Using the current preponderance of evidence standard (essentially 50/50) for those remaining 990 cases would result in 495 innocent and 495 falsely guilty verdicts, with a positive-predictive value of a trial at only 2% that a guilty verdict has identified a guilty physician. Increasing to the 95% standard improves the rate to 17% (only 50 of 990 who are not guilty will be found guilty). By changing the evidentiary standards, the authors believe there could be an 8- to 9-fold reduction in the number of trials wrongly finding innocent physicians guilty of medical malpractice.
Conclusions: Adopting a different evidence standard should be considered. The new standard would not necessarily limit compensation for injuries in cases in which there was negligent practice, but rather limit the number of improper judgments.
Reviewer's Comments: The authors make the point that the approach to malpractice reform needs to take place before the verdict and suggest changing the rules of evidence. Others have argued for more stringent rules of what constitutes expert witnesses or even the utilization of medical tribunals, rather than juries, to hear the evidence. In all cases, the emphasis is on pre-verdict decisional intervention rather than post-verdict economic limitations. (Reviewer-Mark F. Ditmar, MD).

Keywords: Malpractice Judgments, Evidence Standard

Print Tag: Refer to original journal article

What Is the PSA Cut Point for Determining Risk of Prostate Cancer?

Initial Prostate Specific Antigen 1.5 ng/mL or Greater in Men 50 Years Old or Younger Predicts Higher Prostate Cancer Risk.

Tang P, Sun L, et al:

J Urol 2010; 183 (March): 946-951

Men aged <50 years who have an initial PSA of ≤1.5 ng/mL have less risk of ultimately developing prostate cancer than men whose initial PSA is >1.5 ng/mL.

Objective: To determine whether the initial prostate-specific antigen (PSA) performed in men age <50 years predicts the risk of ultimately developing prostate cancer in both black men and white men.
Participants/Methods: Approximately 3500 black men and 6100 white men aged ≤50 years and with a PSA <4 ng/mL were retrospectively analyzed. Patients were divided into groups based upon the initial PSA determination. Univariate and age-adjusted multivariate logistic regression was performed in these men to estimate the risk of developing prostate cancer in the different PSA groups.
Results: In both black and white men, the median initial PSA was 0.7 ng/mL. In both black and white men with an initial PSA value >1.5 ng/mL, the age-adjusted prostate cancer risk increased significantly to 9.3- and 6.7-fold, respectively. At 9 years of follow-up, a PSA cut-off of ≥1.5 ng/mL in men aged <50 years appeared to be the best cut point for increased risk of developing prostate cancer in both black and white men.
Conclusions: The authors believe that an initial PSA cut point of 1.5 ng/mL determines the risk of the subsequent development of prostate cancer in both white and black men aged <50 years.
Reviewer's Comments: Several prior papers have noted that an initial PSA value in men aged <50 years, which is greater than the median in 40- to 49-year-old men, predicts the subsequent risk of prostate cancer. The National Comprehensive Cancer Network recommends that men <50 years of age with a baseline PSA >0.6 ng/mL, which is the median in 40 to 49 year old men, undergo annual screening thereafter. The current paper looks at this recommendation for basing clinical decisions on the median PSA and concludes that a 1.5 ng/mL cut-off in these men is better than the 0.6 ng/mL value. As with many other similar papers, this study is retrospective and does not evaluate prostate cancer family history. In addition, no digital rectal examination results were analyzed. Finally, prostate biopsy rates in the varying PSA subgroups were not specified. It does appear that, if you are between 40 and 49 years of age, the lower your PSA value, the less risk you have of developing prostate cancer. Whether the cut point value should be 0.6 ng/mL or 1.5 ng/mL is not yet clear. Determining a cut point is not trivial because it may signify that patients with a PSA below some value do not need to have as intensive surveillance as men who have values above a cut point. Deciding on a cut-point value may ultimately avoid unnecessary PSA testing and improve cost effectiveness of screening. (Reviewer-George S. Benson, MD).

Keywords: PSA Screening, Prostate Cancer, Cancer Risk

Print Tag: Refer to original journal article

Consider GB for Morbidly Obese Adolescents

Laparoscopic Adjustable Gastric Banding in Severely Obese Adolescents: A Randomized Trial.

O'Brien PE, Sawyer SM, et al:

JAMA 2010; 303 (February 10): 519-526

Gastric banding is significantly more successful for weight loss than a lifestyle program for morbidly obese adolescents.

Background: Almost 20% of adolescents in the U.S. are obese, and this proportion is increasing. Weight loss programs emphasizing lifestyle changes have been largely unsuccessful. Bariatric surgery, including laparoscopic adjustable gastric banding, has been generally more successful than lifestyle changes for weight loss in adults.

Objective: To determine if gastric banding in obese adolescents results in more weight loss than a program emphasizing lifestyle changes.

Design: Prospective randomized controlled trial.

Participants: 50 adolescents between 14 and 18 years of age with a body mass index (BMI) >35 kg/m2, identifiable medical complications, physical limitations, or psychosocial difficulties, and weight loss attempts through lifestyle changes for >3 years were included.

Methods: Patients completed a 2-week food and activity diary, clinical and laboratory assessment, and a 2-month educational program about healthy eating and physical activity. Patients were then randomized to gastric banding (GB) or a lifestyle program (LP). LP participants started an individualized diet (800 to 2000 calories/day), with increased activity (target of >10,000 steps/day). Each LP participant also had a personal trainer for 6 weeks. GB participants had the LAP-BAND adjustable gastric banding system placed. Eating rules after the procedure included ≤3 small (125 mL each) protein-containing meals/day, eaten slowly and chewed well. GB participants were encouraged to exercise >30 minutes/day and remain active. Band adjustments were made during office visits. All participants were followed every 6 weeks for 2 years. The primary outcome measure was weight loss, with the goal being the loss of 50% of excess body weight.

Results: 24 of 25 GB participants and 18 of the 25 LP participants completed the study. Participants were statistically similar in baseline demographics, anthropometric, clinical, and laboratory measurements. Twenty-one (84%) of the GB participants and 3 (12%) of the LP participants lost >50% of excess body weight. Mean weight loss was 34.6 kg (28.3% of total body weight) in the GB group and 3 kg (3.1% of total body weight) in the LP group. Insulin resistance and symptoms of metabolic syndrome improved to a greater degree in the GB group. Eight GB patients required surgical revisions or replacements of the band. In quality-of-life measures, both groups had significant improvements in general health. The GB group also had improved family activities, physical function, self-esteem, and change in health.

Conclusions: GB resulted in significant weight loss in the majority of obese adolescents and was significantly more successful in resulting in weight loss than a lifestyle program.

Reviewer's Comments: GB is currently a last resort for morbidly obese patients. It requires long-term and frequent follow-up by trained professionals to assure that the patient is not overeating. Given the relatively high success rates that have been demonstrated, GB is likely going to become a viable option for selected morbidly obese adolescents. (Reviewer-Rachel Moon, MD).

Keywords: Bariatric Surgery, Obesity

Print Tag: Refer to original journal article

New Ophthalmic Antibiotic for Bacterial Conjunctivitis

Efficacy and Safety of Azithromycin 1.5% Eye Drops for Purulent Bacterial Conjunctivitis in Pediatric Patients.

Bremond-Gignac D, Mariani-Kurkdjian P, et al:

Pediatr Infect Dis J 2010; 29 (March): 222-226

Azithromycin 1.5% ophthalmic drops are effective for the rapid microbiologic and clinical cure of bacterial conjunctivitis.

Objective: To determine the effectiveness of twice daily dosing of azithromycin 1.5% ophthalmic drops for bacterial conjunctivitis in pediatric patients.
Design: Multicenter multinational randomized parallel-group investigator-masked study.
Participants/Methods: The pediatric population (n=150) was a subset of a larger adult and child study. This study was unblended, and no placebo was used due to the different dosing schedule. The azithromycin drops were given 1 drop twice a day for 3 days. Tobramycin drops were given 1 drop every 2 hours while awake for 2 days, and then 4 times daily for 5 days. Clinical cure was determined by the clinical appearance of the eye 9 days after infection and treatment was started. Microbiology swabs were taken on days 0 and 3 except for those patients aged <3 years. Adverse events with drops were recorded.
Results: This subset of 150 patients was taken from the larger study that had >1000 people. Nine patients did not complete the study. On day 1 of the study, 39% of the patients had a positive culture (25 in the azithromycin group and 33 in the tobramycin group). *Haemophilus* was the predominant bacteria in both groups. Overall, 80% of the azithromycin group and 81% of the tobramycin group were clinically cured at the day 9 visit. The clinical cure on day 3 was 48% in the azithromycin group and 27% in the tobramycin group. Microbiologic cure at day 3 was 94% for azithromycin and 76% for tobramycin. Only 3 patients complained with eye stinging/burning (2 in the tobramycin group and 1 in the azithromycin group).
Conclusions: Azithromycin 1.5% ophthalmic drops are effective for the rapid microbiologic and clinical cure of bacterial conjunctivitis.
Reviewer's Comments: There are currently many effective ophthalmic drops on the market for the treatment of bacterial conjunctivitis. Azithromycin with 6 doses in 3 days was very successful in the treatment of conjunctivitis. Children who are a challenge to get drops in their eyes may benefit from this drug's dosing schedule. The national shortage of erythromycin ointment has led many to use tobramycin as an alternative in the nursery. Perhaps with additional testing, azithromycin drops (a macrolide, like erythromycin) could be an alternative to tobramycin and have a broader spectrum than erythromycin for ophthalmic prophylaxis after delivery. (Reviewer-Charles I. Schwartz, MD).

Keywords: Bacterial Conjunctivitis, Treatment, Azithromycin

Print Tag: Refer to original journal article

Will Noninsulin Antidiabetic Medications Added to Metformin Reduce HbA1c?

Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes.

Phung OJ, Scholle JM, et al:

JAMA 2010; 303 (April 14): 1410-1418

Metformin is currently recommended as the first-line medication in patients with type 2 DM. This study suggests that any noninsulin antidiabetic medication added to metformin will reduce HbA_{1c}.

Background: The American Diabetes Association (ADA) currently recommends metformin as initial pharmacotherapy for type 2 diabetes mellitus (DM). Guidelines recommend the addition of a sulfonylurea or insulin if metformin is insufficient to reach glycemic goals. Two other medications, pioglitazone (Actos) and exenatide (Byetta), are specifically recommended in the setting of particular indications (concern about hypoglycemia or weight gain, respectively), but a growing list of other medications has not yet been specifically incorporated into existing ADA guidelines.
Objective: To evaluate the efficacy of a variety of antidiabetic drugs in combination with a stable dose of metformin in patients with type 2 DM.
Design: Systematic review.
Methods: The authors selected randomized clinical trials (RCTs) of patients with type 2 DM treated with metformin who were (a) inadequately controlled on metformin alone, and (b) randomized to an additional noninsulin antidiabetic drug. Included studies were of at least 12 weeks duration and reported glycated hemoglobin (HbA_{1c}) as an outcome. Only good quality studies (according to the Jadad scale) were included (Jadad score of ≥3 on a scale of 5).
Results: 27 trials were included in the meta-analysis after careful review (nearly 12,000 study subjects). All classes of noninsulin antidiabetic medications resulted in significant reductions in HbA_{1c} compared with metformin alone. The authors found no evidence of publication bias (most commonly due to unpublished negative trials), increasing confidence in the significance and magnitude of the HbA_{1c} reductions observed. Use of sulfonylureas, glinides (such as nateglinide [Starlix]) and thiazolidinediones (such as pioglitazone [Actos]) was associated with weight gain. Glucagon-like peptide-1 (GLP-1) analogs, such as exenatide (Byetta) were associated with significant weight loss. Sulfonylureas and glinides were associated with significantly increased risk of hypoglycemia. Dipeptidyl peptidase-4 (DDP-4) inhibitors, such as sitagliptin (Januvia), or α-glucosidase inhibitors, such as acarbose (Precose) were not associated with weight gain, weight loss, or hypoglycemia.
Conclusions: All noninsulin antidiabetic medications evaluated were effective at lowering HbA_{1c}.
Reviewer's Comments: There is a sudden dizzying explosion of new medications to consider in the treatment of type 2 DM, driven by a growing understanding of the cellular mechanisms of insulin sensitivity and insulin secretion, and accelerated by market forces. This study found that all classes of noninsulin antidiabetic medications reduced HbA_{1c} to a comparable extent. Avoid sulfonylureas or glinides in the setting of significant risk of hypoglycemia. Avoid thiazolidinediones, glinides, and sulfonylureas when weight gain poses particular risk. The thiazolidinediones should be particularly avoided in the setting of congestive heart failure. GLP-1 analogs are associated with significant weight gain. As always, side effects, patient acceptance, and cost should remain important considerations. (Reviewer-Paul R. Sutton, PhD, MD).

Keywords: Metformin, Noninsulin Antidiabetic Medications

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