

A Decade of Reversal

	Article	Date of Publication	How it contradicted existing medical practice?
1	Vaccinations and the Risk of Relapse in Multiple Sclerosis	2/1/01	Longstanding concerns about vaccinations preceding the onset or relapses of multiple sclerosis have led to clinician reluctance to give vaccinations to these patients ¹ . In this observational, multicenter, case-crossover study in patients with multiple sclerosis, there was no increased risk of relapse in the two-month period immediately following tetanus, hepatitis B or influenza vaccination.
2	Hepatitis B Vaccination and the Risk of Multiple Sclerosis	2/1/01	Several cases of multiple sclerosis developing within weeks after receiving a new hepatitis B vaccination raised safety concerns about the vaccination, eventually leading to the French government's suspension of a school-based hepatitis B vaccination program ^{2,3} . In a nested case-control study of two large cohorts of nurses, no association was found between receiving the hepatitis B vaccination and the development of multiple sclerosis.
3	Lack of Effect of Induction of Hypothermia after Acute Brain Injury	2/22/01	Since the 1930s, small studies and laboratory investigations have suggested that hypothermia after acute brain injury is an effective therapy ⁴ . Although these data were not strong, many centers began to cool patients routinely despite the effort this required ⁴ . This prospective, multicenter, randomized controlled trial found no benefit for such cooling, contradicting a decades old practice.
4	Initial Plasma HIV-1 RNA Levels and Progression to AIDS in Women and Men	3/8/01	The initial viral load after seroconversion in men with HIV-1 predicts the progression to AIDS ^{5,6} , although it is unclear if this is also true in women. Current guidelines recommend initiating antiretroviral therapy based on viral load in both women and men ⁷ . This study found that although the initial HIV-1 viral load was lower in women, rates of progression to AIDS was similar and that guidelines based on viral load rather than CD4 count leads to treatment differences based on sex.
5	The Teratogenicity of Anticonvulsant Drugs	4/12/01	Two medical textbooks and one review article ⁸ have doubted that anticonvulsants taken during pregnancy are more teratogenic than epilepsy itself. This ⁹ large observational study found that contrary to this position, a systematic examination of infants reveals anticonvulsants during pregnancy increase the risk of fetal malformation.
6	Effect of Early or Delayed Insertion of	4/19/01	Current guidelines recommend insertion of tympanostomy tubes in children with otitis media with effusion of greater than three months

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	Tympanostomy tubes for Persistent Otitis Media on Developmental Outcomes at the Age of Three Years		duration, due to concerns of associated conductive hearing loss leading to developmental impairments ¹⁰ . This randomized study did not find any difference in developmental outcomes in children 3 years old or younger with otitis media with effusion that had prompt tympanostomy tube placement versus delayed placement up to 9 months later if effusion persisted.
7	The Effect of Chelation Therapy with Succimer on Neuropsychological Development in Children Exposed to Lead	5/10/01	Although oral lead chelation therapy with succimer had been implemented, its effect on preventing cognitive impairments in children with moderately elevated blood lead levels is unknown ¹¹ . This randomized, placebo-controlled trial did not find a significant difference in cognitive or behavioral outcomes in children with moderately elevated blood levels treated with succimer.
8	Long-Term Effects of Indomethacin Prophylaxis in Extremely-Low-Birth-Weight Infants	6/28/01	Prophylactic indomethacin treatment in extremely-low-birth-weight infants reduces the frequency of patent ductus arteriosus and severe intraventricular hemorrhage ¹² , although little is known about the long-term effects of this treatment. This randomized, placebo-controlled trial showed that extremely-low-birth-weight infants receiving this treatment did not have any improvements in survival without neurosensory impairment at 18 months.
9	Two Controlled Trials of Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease	7/12/01	Many patients with persistent symptoms of Lyme disease receive prolonged courses of antibiotics, although the effectiveness of this practice remains unknown ¹³ . This randomized, placebo-controlled, double-blinded trial failed to show any significant improvement in symptoms after a prolonged 90-day course of antibiotics in patients with persistent symptoms.
10	Three Months versus One Year of Oral Anticoagulant Therapy for Idiopathic Deep Venous Thrombosis	7/19/01	Studies have shown that treatment for an idiopathic deep venous thrombosis (DVT) with oral anticoagulation therapy for greater than three months reduces the risk of recurrent DVT while on therapy, although it is unclear if this benefit continues once anticoagulation is stopped ¹⁴ . This multicenter, randomized trial showed that a prolonged course of oral anticoagulation following an idiopathic DVT delayed but did not reduce the long-term risk for a recurrent DVT when compared to a three-month course of treatment.
11	Failure of Metronidazole to Prevent Preterm Delivery among Pregnant Women with Asymptomatic	8/16/01	Recommendations have been made for the screening and treatment of asymptomatic <i>Trichomonas vaginalis</i> infections in pregnant women in order to prevent low birth weight and preterm birth ¹⁵ . In this randomized trial, treatment of asymptomatic <i>Trichomonas</i> with metronidazole

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	<i>Trichomonas vaginalis</i> Infection		during pregnancy was actually significantly associated with an increase risk of preterm birth.
12	Effect of Prone Positioning on the Survival of Patients with Acute Respiratory Failure	8/23/01	Prone positioning in ventilated patients with acute lung injury or acute respiratory distress syndrome improves oxygenation and has been increasingly utilized ¹⁶ . However, this multicenter, randomized trial failed to show any survival benefit of the prone position compared to the supine position in ventilated patients with these conditions.
13	Medical Treatment for Neurocysticercosis Characterized by Giant Subarachnoid Cysts	9/20/01	Surgery is considered the treatment of choice for the helminthic infection neurocysticercosis when it is associated with giant cysts and intracranial hypertension ¹⁷ . In this series of patients with neurocysticercosis with giant cysts and intracranial hypertension, intensive medical therapy with corticosteroids and the antihelminthic drugs albendazole and praziquantal resulted in clinical improvement in all patients, suggesting that surgery may not be needed in all such patients.
14	Naltrexone in the Treatment of Alcohol Dependence	12/13/01	Naltrexone is an opioid-receptor antagonist that is FDA-approved for the treatment of alcohol dependence, although its efficacy is uncertain ^{18, 19} . In this multicenter, double-blind, placebo-controlled study, naltrexone used as an adjunct to standardized psychosocial treatment failed to have any significant effect on the treatment of alcohol dependence.
15	Comparison of Two Diets for the Prevention of Recurrent Stones in Idiopathic Hypercalciuria	1/10/02	A low-calcium diet is widely recommended for patients with a history of kidney stones and idiopathic hypercalciuria ²⁰ . Theoretically, this would lower the concentration of calcium in the urine, prevent supersaturation, and decrease stone formation. This trial ²¹ randomized such patients to a low-calcium diet or a diet low in animal protein and salt (but with normal calcium). At 5 years they found nearly double the risk of recurrence in the low-calcium diet group.
16	Frequency of Uterine Contractions and the Risk of Spontaneous Preterm Delivery	1/24/02	Ambulatory monitoring of uterine contractions continues in the United States despite evidence suggesting it does not improve the rate of preterm delivery ²² . This observational study formally assessed the test characteristics of frequent contractions in predicting early delivery found no threshold had good sensitivity and reasonable positive predictive value, further undermining ongoing practice.
17	Screening of Infants and Mortality Due to Neuroblastoma	4/04/02	Mass screening of infants for neuroblastoma had been done as part of pilot studies in the U.K., France, Austria, Australia, U.S.A., Italy, Norway and Germany ²³ . In Japan, screening was instituted in the 1970s, with over 7 million children undergoing screening, and 650 cases of

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			neuroblastoma found by the 1990s ²³ . This large population study of 476,654 children in Canada found this practice did not decrease mortality from neuroblastoma. ²⁴ The study also makes us question another handful of newborn and infant screening, which remains untested ²⁵ .
18	Neuroblastoma Screening at One Year of Age	4/04/02	Mass screening of infants for neuroblastoma had been done as part of pilot studies in the U.K., France, Austria, Australia, U.S.A., Italy, Norway and Germany ²³ . In Japan, screening was instituted in the 1970s, with over 7 million children undergoing screening, and 650 cases of neuroblastoma found by the 1990s ²³ . This large population study of 2.5 million children in Germany found this practice did not decrease mortality from neuroblastoma. ²⁶
19	Immediate Repair Compared with Surveillance of Small Abdominal Aortic Aneurysms	5/09/02	For over a decade, vascular surgery societies had recommended elective repair of aneurysms of 4.0 cm or more in diameter for patients without medical contraindications ²⁷ . This randomized trial examined patients with aneurysms between 4.0 and 5.4 cm in diameter. It found no improvement in mortality for this procedure compared to observation, even though elective operative mortality was low ²⁸ .
20	Intranasal Mupirocin to Prevent Postoperative <i>Staphylococcus aureus</i> Infections	6/13/02	Patients who carry <i>Staph Aureus</i> in their nasal passages are more likely to have surgical site infections, often with the same isolate they are colonized with. Several previous studies ^{29, 30} showed that intranasal mupirocin can decrease the rate of surgical site infection among such patients compared to historical controls. This randomized control trial ³¹ however, found that the prophylactic intranasal application of mupirocin did not significantly reduce the rate of <i>Staph Aureus</i> surgical-site infections.
21	A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee	7/11/02	650,000 arthroscopic knee surgeries were performed annually in the US at a cost of \$5000 dollars each at the time of this randomized trial. ³² This study found that the intervention performed no better than a placebo intervention on the outcome of pain and function.
22	Twenty-Five-Year Follow-up of a Randomized Trial Comparing Radical Mastectomy, Total Mastectomy, and Total Mastectomy Followed by Irradiation	8/22/02	Radical Halsted Mastectomy (RHM) rose to prominence without randomized controlled trials supporting its efficacy. This 25 year follow-up of a large randomized study ³³ comparing RHM to mastectomy with radiation, or mastectomy with sentinel node dissection and axillary node removal only if positive found that less aggressive surgical techniques had similar mortality outcomes. Thus, the trial failed to show benefit for a more aggressive surgery, which dominated medicine in the 20 th century
23	Sex-Based	10/31/02	In 1997, a randomized trial found that digitalis

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	Differences in the Effect of Digoxin for the Treatment of Heart Failure		decreased the rate of hospitalization for patients with heart failure with no adverse (or beneficial) effect on mortality ³⁴ . Because of these results, the American College of Cardiology ³⁵ , European Society of Cardiology ³⁶ , and the Heart Failure Society of America ³⁷ all recommend this medication for all patients. However, whether the effect differs in men and women was unknown. This analysis ³⁸ found that digitalis increases the rate of death among women.
24	Antimicrobial Treatment in Diabetic Women with Asymptomatic Bacteriuria	11/14/02	In contrast to Europe, in the United States, several groups ^{39, 40} recommended screening and treating asymptomatic bacteriuria among women with diabetes. This randomized trial found although this practice leads to more antibiotic use, it did not reduce complications or improve the time to symptomatic infection.
25	A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation	12/5/02	Many physicians treat patients with atrial fibrillation with costly anti-arrhythmic drugs in a strategy to maintain sinus rhythm. While this approach has a physiologic rationale, and improves some surrogate endpoints, it has not been proven to improve survival. The AFFIRM study ⁴¹ showed that a strategy of rate control yielded similar mortality outcomes, and fewer adverse drug reactions.
26	A Comparison of Rate Control and Rhythm Control in Patients with Recurrent Persistent Atrial Fibrillation	12/5/02	For many patients with atrial fibrillation, management strategies focus on maintaining sinus rhythm, often with repeat electric cardioversion and prophylactic anti-arrhythmic drugs ⁴² . This study ⁴³ found no benefit with respect to mortality for a rhythm as opposed to rate control strategy.
27	A Randomized, Controlled Trial of the Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients	1/2/03	The pulmonary artery catheter (PAC) is frequently used for hemodynamic monitoring in the intensive care unit. There has not been a definitive randomized controlled trial to evaluate the clinical value of this monitoring device. At the time of this article, more than 1.5 million PACs were placed in North America annually ⁴⁴ . This study evaluated this claim through 3803 patients randomized to surgery with PAC vs. surgery without if ICU stay was anticipated. There was no benefit to therapy directed by PAC over standard care in elderly, high-risk patients post operatively.
28	Imaging Studies after a First Febrile Urinary Tract Infection in Young Children	1/16/03	In children between the ages of 2 and 24 months who present with a UTI, the American Association of Pediatrics recommends a voiding cystourethrogram and renal ultrasound ⁴⁵ . This study evaluated this practice in a prospective cohort. It sought to determine whether imaging studies altered management or improved outcomes in children with a first febrile urinary tract infection. This study found that an ultrasound

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29	Serum Retinol Levels and the Risk of Fracture	1/23/03	<p>in this clinical setting is almost always normal (88%), and if abnormal, clinical management was unchanged (Reversal) If voiding cystourethrogra was abnormal, non-evidence based strategies were offered (thus no conclusion can be drawn) Many nations fortify foods with Vitamin A in hopes of preventing Vitamin A deficiency, which is rare and associated with night blindness xerophthalmia and keratomalacia⁴⁶. In Sweden, margarine and other dairy products are fortified⁴⁷ This study sought to determine whether there is an elevated fracture risk in patients with elevated vitamin A levels. This study found that the risk of fracture was highest among men with the highest levels of serum retinol (a marker of vitamin A ingestion). This suggests that the current practice of Vitamin A supplementation and food fortification ought be re-evaluated.</p>
30	Factors Associated with Progression of Carcinoid Heart Disease	3/13/03	<p>One of the treatments currently being used for metastatic midgut carcinoid tumors are cytotoxic chemotherapeutic agents. The data supporting this intervention is dubious^{48, 49}. The current retrospective investigation⁵⁰ found cytotoxic agents to be a strong risk factor for carcinoid heart disease, despite reduction in 5-HIAA in many patients. Thus, an intervention of dubious efficacy is found to potentially have a significant harm.</p>
31	Effects of Estrogen plus Progesterin on Health-Related Quality of Life	5/8/03	<p>Hormone replacement therapy with estrogen and progesterin has been reported to improve vasomotor symptoms^{51, 52}. As such, these hormones have been used by women to improve quality of life after menopause^{53, 54}. This Women's Health Initiative study evaluated the use of estrogen plus progesterin on quality of life. There was no significant effect on health, vitality, mental health, depressive symptoms or sexual satisfaction in the hormone arm as compared to placebo.</p>
32	Involved-Field Radiotherapy for Advanced Hodgkin's Lymphoma	6/12/03	<p>Despite dramatic changes in the management of Advanced Hodgkin's disease over the last 2 decades, many physicians continue to treat these patients with radiation therapy. They cite data that shows it decreases local recurrence⁵⁵. Even free and overall survival were not significantly different, and, if anything, favored the omission of radiotherapy.</p>
33	Conventional Adjuvant Chemotherapy with or without High-Dose Chemotherapy and Autologous Stem-Cell Transplantation in High-Risk Breast Cancer	7/3/03	<p>Multiple studies have claimed that high dose chemotherapy with stem cell transplantation improves disease free survival at 3 years to 65-70%, an improvement of 20-30% beyond standard adjuvant chemotherapy^{56, 57}. High dose chemo and stem cell transplant became a common, costly and controversial practice for more than a decade. This trial randomized patients with primary breast cancer with at least 10 ipsilateral axillary lymph</p>

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			nodes to standard adjuvant chemotherapy vs. adjuvant chemotherapy followed by high dose chemotherapy and stem cell transplantation. The study arm was found to reduce risk of relapse but no improvement in survival was found.
34	A Multicenter, Randomized, Double-Blind, Controlled Trial of Nebulized Epinephrine in Infants with Acute Bronchiolitis	7/3/03	Multiple studies have demonstrated improved short-term outcomes after epinephrine administration in infants with acute bronchiolitis ⁵⁸⁻⁶⁰ . This randomized, double blind trial compared nebulized epinephrine with placebo in 194 infants with bronchiolitis. There was no significant difference in length of hospitalization, a more meaningful endpoint, between the groups
35	Evaluation of Impermeable Covers for Bedding in Patients with Allergic Rhinitis	7/17/03	The encasement of bedding with impermeable covers has been recommended for the treatment of allergic rhinitis ^{61, 62} . These recommendations are part of an effort to reduce exposure to house-dust mites. This study evaluated this recommendation by randomly assigning 279 patients with allergic rhinitis to impermeable vs. permeable bedding covers. There was a reduction in allergen emission from mattresses in the impermeable group but no effect on clinical outcomes.
36	Control of Exposure to Mite Allergen and Allergen-Impermeable Bed Covers for Adults with Asthma	7/17/03	The cost of impermeable bed covers is in the millions of dollars annually, while the cost of all preventive interventions for asthma and allergic rhinitis is in the billions ⁶³ . US ⁶⁴ and European ⁶⁵ guidelines recommend these covers be used among many patients with asthma. This double-blind, randomized, placebo-controlled trial of over 1100 patients found no benefit on any clinical or physiologic outcome for this practice.
37	Estrogen plus Progestin and the Risk of Coronary Heart Disease	8/7/03	Observational studies suggested that post-menopausal hormonal replacement would decrease coronary artery disease ⁶⁶ . This study randomized postmenopausal women to either estrogen/progesterone vs. placebo to evaluate this claim. After a 5.2 year follow up, no cardiac protection was found and CHD risk was potentially elevated in the first year of use.
38	Hormone Therapy and the Progression of Coronary-Artery Atherosclerosis in Postmenopausal Women	8/7/03	Observational studies suggested that post-menopausal hormonal replacement would decrease coronary artery disease ⁶⁶ . This study found that these medications do not slow the progression of coronary artery disease.
39	Outcomes at School Age after Postnatal Dexamethasone Therapy for Lung Disease of Prematurity	3/25/04	Postnatal dexamethasone has long been practiced to prevent or treat chronic lung disease in premature newborns ⁶⁷ , but the long-term developmental side effects are unknown. This double-blind, placebo-controlled trial of early postnatal dexamethasone therapy (within 12 hours

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			of birth) showed that this therapy led to significantly more delays in somatic growth (head circumference and height), poorer neuromotor and cognitive function (including IQ scores) and more clinically significant disabilities when the children became of school-age.
40	C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease	4/1/04	Measuring C-reactive protein (CRP) to evaluate for the risk of coronary atherosclerosis has been supported by 2003 consensus statements from the Centers for Disease Control and Prevention and the American Heart Association ⁶⁸ . A prospective cohort study from patients in Reykjavik, Iceland showed that CRP was only a relatively moderate predictor of the risk of coronary artery disease and added only marginally to the predictive value of established risk factors. The authors called for the recent recommendations from the CDC and AHA to be reviewed on the basis of their findings.
41	The Influence of Resection and Aneuploidy on Mortality in Oral Leukoplakia	4/1/04	THIS PAPER WAS ITSELF RETRACTED IN NEJM 2006 b/c of possible falsified data
42	A Comparison of High-Dose and Standard-Dose Epinephrine in Children with Cardiac Arrest	4/22/04	The American Heart Association 2000 guidelines for pediatric advanced life support recommended that rescue doses of epinephrine (i.e. those subsequent to the initial dose) during cardiopulmonary resuscitation be at the standard dose (0.01 mg per kg of body weight) or a higher dose (0.1 mg per kg) ⁶⁹ . In this prospective, randomized, double-blind trial that compared high dose to standard dose epinephrine for rescue therapy, there was no benefit of high dose therapy in the rate of return of spontaneous circulation for in-hospital cardiac arrests. High dose epinephrine also led to a lower rate of survival within 24 hours and a lower rate of survival to hospital discharge as compared to the standard dose.
43	Open Mesh versus Laparoscopic Mesh Repair of Inguinal Hernia	4/29/04	A laparoscopic approach to repair inguinal hernias with mesh was thought to have lower hernia recurrence rates and less post-operative pain ^{70, 71} . This multicenter, randomized trial in a VA population found that the laparoscopic approach led to a higher rate of complications and a higher rate of recurrences when repairing primary inguinal hernias.
44	Folate Therapy and In-Stent Restenosis after Coronary	6/24/04	Previous studies ^{72, 73} have suggested that folate therapy (folic acid, Vitamin B6, and Vitamin B12) reduce homocysteine levels which thereby lower

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	Stenting		the rate of coronary atherosclerosis. One such clinical study ⁷² found that folate therapy reduced the rate of restenosis after coronary angioplasty which led some interventionalists to adopt the use of this therapy. This double-blind, placebo-controlled randomized trial conducted in Germany and the Netherlands showed that contrary to previous findings, folate therapy actually increased the restenosis rate and increased the need for repeat revascularization after a coronary intervention was performed.
45	Methylprednisolone, Valacyclovir, or the Combination for Vestibular Neuritis	7/22/04	The etiology of vestibular neuritis is presumed to be a viral infection ⁷⁴ and yet it is unknown whether steroids, an anti-viral or a combination of both have any benefit in treating this disease. At the time of this publication, physicians prescribed either or both. A prospective, randomized, double-blind, two-by-two factorial trial was performed assessing whether placebo, methylprednisolone, valacyclovir or a combination of the two would improve symptoms. Only the steroid and not the anti-viral improved the recovery of patients with vestibular neuritis.
46	Lumpectomy plus Tamoxifen with or without Irradiation in Women 70 Years of Age or Older with Early Breast Cancer	9/2/04	Several breast cancer trials have shown that post-operative irradiation decreases the rate of ipsilateral recurrence but does not affect rate of survival ^{75, 76} yet was still being used in clinical practice. Women over the age of 70 years old with estrogen receptor positive breast cancer in this randomized study received no benefit with lumpectomy plus tamoxifen and irradiation compared to lumpectomy plus tamoxifen alone, as the five year survival rates and rates of distant metastases were no different in the two groups.
47	Fresh Whole Blood versus Reconstituted Blood for Pump Priming in Heart Surgery in Infants	10/14/04	In an attempt to decrease the coagulopathic and inflammatory changes seen during cardiopulmonary bypass surgery, pediatric cardiothoracic surgeons have opted to use fresh whole blood during congenital heart operations for their neonate and infant patients ^{77, 78} , thus becoming the standard of care. However, this single-centered, randomized, double-blind controlled trial showed that fresh whole blood had no advantage over reconstituted blood (i.e. combination of packed red cells and fresh-frozen plasma) during surgery for this pediatric population. Additionally, the use of whole blood led to increased ICU length of stay and increased post-operative fluid overload.
48	Angiotensin-Converting-Enzyme	11/11/04	For patients with vascular disease, but without HF, the HOPE ⁷⁹ and EUROPA ⁸⁰ trials suggested a

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	Inhibition in Stable Coronary Artery Disease		benefit of ace-inhibitors. Because of these studies, many physicians began prescribing ace-inhibitors widely for patients with vascular disease—beyond the inclusion criteria of these studies, or utilizing different medications in the same class ⁸¹ . The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial demonstrated that patients with stable coronary artery disease and preserved left ventricular function who are already on current standard therapy do not benefit with the addition of trandolapril. In this low risk population, the addition of an ACE-inhibitor did not reduce rates of cardiovascular death, myocardial infarction or coronary revascularization.
49	Secondary Surgical Cytoreduction for Advanced Ovarian Carcinoma	12/9/04	Several prospective studies and one randomized trial ⁸² have shown that for women with advanced ovarian carcinoma who were treated with primary cytoreductive surgery and chemotherapy, but who were subsequently found to have recurrent disease, secondary surgical cytoreduction, improves progression-free and overall survival. However, in the prior RCT, not all patients underwent a primary maximal debulking surgery. Thus, in clinical practice, patients who were previously maximally debulked, and treated with chemo, were being debulked again. This randomized trial found that secondary surgical cytoreduction after chemotherapy did not improve progression-free survival or overall survival rates compared to chemotherapy alone in those whose primary debulking surgery was maximal.
50	Coronary-Artery Revascularization before Elective Major Vascular Surgery	12/30/04	Many clinicians perform routine coronary-artery revascularization prior to vascular surgery in order to improve preoperative risk in patients with stable disease, even deviating from published guidelines ⁸³ . This randomized, multicentered VA trial revealed that coronary artery revascularization in patients with stable disease before undergoing elective vascular surgery did not offer any benefit.
51	Mild Intraoperative Hypothermia during Surgery for Intracranial Aneurysm	1/13/05	Hypothermia was found to be helpful as a neurosurgical adjunct in 1955, especially for ischemic and traumatic insults. At the time of this publication, it was being used in nearly 50% of aneurysm surgeries ⁸⁴ . This large randomized study, the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), showed no improvement in neurologic outcomes with hypothermia, and an increase in bacterial infections.
52	Clopidogrel versus	1/20/05	Joint American College of Cardiology and

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	Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding		American Heart Association guidelines recommended that patients who have had GI bleeding while on aspirin consider the use of clopidogrel or the addition of a PPI ⁸⁵ . While the guidelines treat both as equivalent strategies, this study showed that aspirin plus esomeprazole was far superior to clopidogrel in preventing future ulcer bleeding.
53	The Risk of Cesarean Delivery with Neuraxial Analgesia Given Early versus Late in Labor	2/17/05	The American College of Obstetrics and Gynecology recommends that epidural anesthesia be delayed until cervical dilation has reached at least 4cm. In the interim, patients are encouraged to use and systemic opioids ⁸⁶ . This recommendation is based on a small randomized trial ⁸⁷ , and a post-hoc analysis of a larger one ⁸⁸ that found an increased risk of cesarean with early epidural anesthesia. The current study showed no difference in the risk of cesarean delivery between the two forms of anesthesia.
54	UK Controlled Trial of Intrapleural Streptokinase for Pleural Infection	3/3/05	Management guidelines ⁸⁹ suggest that intrapleural fibrinolytics help the drainage of infected pleural effusions and reduce the need for surgical drainage. This study, the First Multicenter Intrapleural Sepsis Trial (MIST1), found no benefit in mortality, need for surgery, or length of hospital stay with intrapleural streptokinase.
55	Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial	3/17/05	Selective COX-2 inhibitors were widely prescribed in lieu of NSAIDs because they demonstrated similar analgesic levels with fewer GI side effects ⁹⁰ . In addition, COX-2 was identified as a promoter of intestinal tumorigenesis and selective COX-2 inhibition was believed to have the potential to prevent colorectal adenomas ⁹¹ . The first study noted here, the Adenomatous Polyp Prevention on Vioxx (APPROVE) Trial, showed an increase in cardiovascular risk with rofecoxib.
56	Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention	3/17/05	The second study, the Adenoma Prevention with Celecoxib (APC) Study, showed a dose-response association with celecoxib use and cardiovascular risk. ²
57	Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery	3/17/05	Selective COX-2 inhibition was previously shown to reduce the need for opioids after surgery without adverse events ⁹² . This study showed that selective COX-2 inhibition for pain control after coronary artery bypass graft surgery was associated with an increased incidence of cardiovascular events.
58	Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis	3/31/05	Anticoagulation for treatment of intracranial arterial stenosis was first used in 1955 and the use of warfarin over aspirin had been supported by retrospective studies ^{93, 94} . Neurologists were found to be evenly divided between warfarin and aspirin

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			use. This study, the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial, showed that warfarin had higher rates of adverse events and no benefit compared to aspirin for intracranial arterial stenosis.
59	Long-Term Outcomes of Coronary-Artery Bypass Grafting versus Stent Implantation	5/26/05	Percutaneous coronary intervention (PCI) has been increasingly used to treat multivessel disease, but few trials compared the two for this indication. This observational study found that CABG is still superior to PCI with stenting for treatment of multivessel disease in a large new York state cohort.
60	Hydroxyurea Compared with Anagrelide in High-Risk Essential Thrombocythemia	7/7/05	Hydroxyurea is first-line therapy for high-risk patients with essential thrombocytosis. Anagrelide was found to decrease platelet counts and was also used as first-line therapy for high-risk patients despite a lack of evidence, and a higher cost. This study showed hydroxyurea plus aspirin to be superior to anagrelide.
61	Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure	7/7/05	Premature infants in respiratory distress who do not respond to surfactant were thought to benefit from inhaled nitric oxide due to pulmonary vasodilation and decreased inflammation. A single-center study showed a decrease in bronchopulmonary disease and death in moderately ill infants ⁹⁵ . This larger, multicenter randomized trial showed no benefit with the use of inhaled nitric oxide for infants weighing less than 1500g.
62	An Evaluation of Echinacea angustifolia in Experimental Rhinovirus Infections	7/28/05	Echinacea has become a popular remedy for the common cold since the Dietary Supplement Health and Education Act in 1994 liberalized the regulation of herbal medicines. This study showed that echinacea held no benefit in symptom duration or severity with rhinovirus infection (common cold).
63	Developmental Outcomes after Early or Delayed Insertion of Tympanostomy Tubes	8/11/05	Official guidelines ⁹⁶ recommended myringotomy with the insertion of tympanostomy tubes to relieve persistent middle ear effusions in children out of concern that conductive hearing loss would lead to adverse effects on cognitive, speech, language, and psychosocial development. This has become one of the most common procedures of childhood. This study showed no difference in development between prompt and delayed tympanostomy tubes.
64	Amnioinfusion for the Prevention of the Meconium Aspiration Syndrome	9/1/05	A systematic review of randomized trials found that amnioinfusion was associated with an overall reduction in meconium aspiration syndrome ⁹⁷ . This study showed that amnioinfusion had no benefit for preventing meconium aspiration syndrome (or other major maternal/neonatal disorders).
65	Early Invasive versus	9/15/05	Several studies comparing early to conservative

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	Selectively Invasive Management for Acute Coronary Syndromes		invasive therapy in acute coronary syndromes showed the benefit of early invasive therapy, but only the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II trial ⁹⁸ showed a reduction in mortality, specifically in men. The American College of Cardiology-American Heart Association guidelines since recommended early invasive therapy for high-risk patients with acute coronary syndromes without ST-segment elevation ⁹⁹ . This study, the Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial, showed no mortality benefit of an early invasive strategy given optimized medical therapy.
66	Long-Term Vasodilator Therapy in Patients with Severe Aortic Regurgitation	9/29/05	An earlier study showed nifedipine delayed the need for surgery in patients with asymptomatic chronic severe aortic regurgitation ¹⁰⁰ and vasodilators have since been given a class I recommendation by the American College of Cardiology-American Heart Association ¹⁰¹ and the European Society of Cardiology ¹⁰² . This study found no benefit with nifedipine or enalapril in reducing or delaying the need for aortic valve replacement and in treatment of aortic regurgitation.
67	Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure	11/10/05	In small single-center trials, continuous positive airway pressure (CPAP) significantly improved disease progression and quality of life. In one trial ¹⁰³ , it also trended toward a reduction in mortality and need for heart transplantation, although this was before the common use of beta blockade in heart failure treatment. Although this study showed numerous benefits for the use of CPAP in central sleep apnea in patients with heart failure, it showed no mortality benefit nor benefit in quality of life.
68	A Trial of Contraceptive Methods in Women with Systemic Lupus Erythematosus	12/15/05	Studies show that estrogens favor development/exacerbation of lupus and that lupus flares can occur in patients taking exogenous estrogens. There are no official guidelines addressing the issue, resulting in hesitance in prescribing contraceptives. It is known that maternal/fetal outcomes are worse if conception occurs during active lupus flares and that there is a high rate of elective abortions in women with lupus ¹⁰⁴ , suggesting the need for appropriate birth control in this population. Both the first study and the second study, the Oral Contraceptives-Safety of Estrogens in Lupus Erythematosus National Assessment (OC-SELENA) Trial, showed that the use of oral contraceptives do not increase the incidence of lupus flares.
69	Combined Oral Contraceptives in	12/15/05	Both the first study and the second study, the Oral Contraceptives-Safety of Estrogens in Lupus

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	Women with Systemic Lupus Erythematosus		Erythematosus National Assessment (OC-SELENA) Trial, showed that the use of oral contraceptives do not increase the incidence of lupus flares.
70	The Risk Associated with Aprotinin in Cardiac Surgery	1/26/06	The majority of patients undergoing surgical treatment for ST-elevation myocardial infarction receive antifibrinolytic therapy to limit blood loss ¹⁰⁵ . In this observational study involving 4374 patients undergoing revascularization, three agents (aprotinin [1295 patients], aminocaproic acid [883], and tranexamic acid [822]) as compared with no agent (1374 patients) were prospectively assessed with regard to serious outcomes by propensity and multivariable methods. Aprotinin was associated with increased risk of renal failure, myocardial infarction or heart failure, and stroke.
71	Clozapine Alone versus Clozapine and Risperidone with Refractory Schizophrenia	2/2/06	Schizophrenia has poor response to any single antipsychotic drug, resulting in the increasing frequency of antipsychotic polypharmacy ¹⁰⁶ . In this randomized, double blind randomized clinical trial patients with poor response to clozapine were randomly assigned to augmentation with risperidone or placebo. The addition of risperidone to clozapine did not improve symptoms in patients with severe schizophrenia
72	Saw Palmetto for Benign Prostatic Hyperplasia	2/9/06	Saw palmetto is used by over 2 million men in the United States for the treatment of benign prostatic hyperplasia ¹⁰⁷ and is commonly recommended as an alternative to drugs approved by the Food and Drug Administration. In this double-blind trial, 225 men over the age of 49 years who had moderate-to-severe symptoms of benign prostatic hyperplasia were randomized to one year of treatment with saw palmetto extract (160 mg twice a day) or placebo. There was no significant difference between the saw palmetto and placebo groups in the change in AUASI scores (mean difference, 0.04 point; 95 percent confidence interval, -0.93 to 1.01), maximal urinary flow rate (mean difference, 0.43 ml per minute; 95 percent confidence interval, -0.52 to 1.38), prostate size, residual volume after voiding, quality of life, or serum prostate-specific antigen levels during the one-year study.
73	Calcium plus Vitamin D Supplementation and the Risk of Fractures	2/16/06	Observational evidence and data from randomized clinical trials suggested that calcium or vitamin D supplements or both may slow bone loss and reduce the risk of falls. However, in this randomized clinical trial involving 36,000 postmenopausal women, calcium with vitamin D supplementation did not significantly reduce hip fracture, and increased the risk of kidney stones
74	Glucosamine, Chondroitin Sulfate,	2/23/06	The dietary supplements glucosamine and chondroitin sulfate had been advocated as safe

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	and the Two in Combination for Painful Knee Osteoarthritis		and effective options for the management of symptoms of osteoarthritis. In this RCT 1583 patients with symptomatic knee osteoarthritis were randomized to receive 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, both glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee.
75	Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome	4/20/06	Moderate dose corticosteroids was thought to improve clinical outcomes in those with persistent ARDS. In this trial 180 patients were randomly assigned to methylprednisolone or placebo. Mortality at 60 days between the two groups was no different, suggesting that steroids should not routinely be used in patients with ARDS
76	Pulmonary-Artery versus Central Venous Catheter to Guide Treatment of Acute Lung Injury	5/25/06	The pulmonary artery catheter (PAC) has been advocated by many to be used in critically ill patients in order to provide real time data on hemodynamic markers, such as central venous pressure and pulmonary artery wedge pressure. This study randomized 1000 patients with established acute lung injury to either a PAC or a central venous catheter (CVC). PAC-guided therapy did not improve survival or organ function but was associated with more complications than CVC-guided therapy.
77	A Controlled Trial of Homocysteine Lowering and Cognitive Performance	6/29/06	Observational studies suggested that plasma homocysteine concentrations are inversely related to cognitive function in older people ¹⁰⁸ , and some clinicians have prescribed folate, B12 and B6 to preserve cognitive function. This double-blind, placebo-controlled, randomized clinical trial involving 276 healthy participants, 65 years of age or older showed that despite intense homocysteine-lowering treatment there was no significant differences between the vitamin and placebo groups in the scores on tests of cognition.
78	Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease	10/12/06	Second-generation (atypical) antipsychotic drugs had been widely used to treat psychosis, aggression, and agitation in patients with Alzheimer's disease ¹⁰⁹ . In this double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received

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			placebo discontinued their assigned treatment owing to intolerability (P = 0.009). No significant differences were noted among the groups with regard to improvement on the CGIC scale. This suggests that adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease
79	DHEA in Elderly Women and DHEA or Testosterone in Elderly Men	10/19/06	DHEA and testosterone were widely promoted as supplements. In this placebo-controlled, randomized, double-blind study men were randomized to placebo, testosterone, or DHEA. Women received either DHEA or placebo. Neither DHEA nor low-dose testosterone replacement in elderly people was shown to have physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life
80	Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease	11/16/06	In 2000, the KDOQI guidelines recommended that the target level of hemoglobin should be 11.0 to 12.0 g per deciliter in patients with chronic kidney disease ¹¹⁰ , whether or not they were receiving dialysis, which was further updated to include an expanded the target range to 11.0 to 13.0 g ¹¹¹ . In this study 1432 patients with chronic kidney disease were studied, 715 of whom were randomly assigned to target a Hg of 13.5g per deciliter and 717 of whom were assigned to target a Hg of 11.3g per deciliter. The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life.
81	Coronary Intervention for Persistent Occlusion after Myocardial Infarction	12/7/06	In patients with acute coronary syndrome and persistent total occlusion of the infarct-related coronary artery after the time of myocardial salvage, there was strong bias in favor of PCI in addition to optimal medical therapy (OMT) ¹¹² . In this randomized clinical trial patients who had total occlusion of the infarct related artery 3 to 28 days after myocardial infarction were randomized to PCI with stenting with OMT versus OMT alone. PCI did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction during 4 years of follow-up
82	Tympanostomy Tubes and Developmental Outcomes at 9 to 11 Years of Age	1/18/07	Originally, it was thought that conductive hearing loss due to persistent otitis media could lead to long-term developmental impairment. ^{113, 114} In fact, official guidelines recommended that children with middle-ear effusion persisting 3 or 4 months have a myringotomy with insertion of tympanostomy tubes. ^{115, 116} This study showed that prompt insertion of tympanostomy tubes in infants with persistent middle-ear effusion did not

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			<p>improve developmental outcomes, measured by literacy, attention, and social skills in children at 9 to 11 years of age.</p>
83	Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden	3/8/07	<p>Many studies had shown that rates of in-stent restenosis were lower with the use of drug-eluting stents compared to bare-metal stents.^{117,118} While the FDA had approved these stents as safe for patients with previously untreated lesions of a certain size, the use of drug-eluting stents expanded to include treatment in more complicated patients with larger lesions.¹¹⁹⁻¹²² This prospective study showed that drug-eluting stents were associated with higher mortality rates compared to bare-metal stents.</p>
84	Influence of Computer-Aided Detection on Performance of Screening Mammography	4/5/07	<p>At the time this article was published, many mammography facilities in the U.S. had adopted computer-aided detection to analyze digitized mammograms and highlight suspicious areas for review by a radiologist.^{123,124} However, this study found that the use of this technology was associated with reduced accuracy of interpretation for screening mammograms and that the increased rates of biopsy associated with computer-aided detection did not necessarily translate to improved detection of invasive breast cancer.</p>
85	Optimal Medical Therapy with or without PCI for Stable Coronary Disease	4/12/07	<p>While treatment guidelines recommended an initial approach of intensive medical therapy, reduction of risk factors, and lifestyle modification (optimal medical therapy) for patients with stable coronary artery disease, percutaneous coronary intervention (PCI) was still a common initial treatment strategy for patients with stable coronary artery disease at the time this study was done.^{125,126} This study found that PCI added to optimal medical therapy did not reduce the risk of death, myocardial infarction or other major cardiovascular events.</p>
86	Effectiveness of Adjunctive Antidepressant Treatment for Bipolar Depression	4/26/07	<p>Even though the FDA had not approved any of the standard antidepressants for treatment of bipolar depression at the time of this study, many antidepressants were used as adjuncts to mood-stabilizers in patients with bipolar depression without significant evidence of the efficacy or potential risks of this treatment modality.¹²⁷⁻¹³⁰ This RCT showed that the use of a standard antidepressant as an adjunctive treatment was not associated with increased efficacy or with increased risk of treatment-related affective switch.</p>
87	Randomized Comparison of Strategies for Reducing Treatment	5/17/07	<p>Treatment guidelines for patients with persistent asthma whose symptoms are well controlled on an inhaled corticosteroid can be stepped down to an alternative, less intensive treatment¹³¹⁻¹³³, such as</p>

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	in Mild Persistent Asthma		a combination long-acting beta agonist and ICS, or an antileukotriene like montelukast ¹³⁴ . This randomized controlled trial showed that patients with asthma that was well controlled with the use of inhaled fluticasone twice daily could be switched to once-daily fluticasone plus salmeterol without increased rates of treatment failure. However, switching to montelukast resulted in increased rates of treatment failure and decreased asthma control.
88	Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes	6/14/07	Rosiglitazone was introduced in 1999 and was approved in type II diabetes mellitus because of its ability to reduce blood glucose and Hgb A1C. ¹³⁵ This study looking at the relationship between use of this drug and risk of cardiovascular disease was done because cardiovascular disease is a common cause of disease in diabetic patients. ¹³⁶ This meta-analysis found that rosiglitazone was associated with a significant increase in the risk of myocardial infarction and a near-significant increase in the risk of cardiovascular-related death and suggest reason for cautious use of this drug in type II diabetics.
89	In Vitro Fertilization with Preimplantation Genetic Screening	7/5/07	Because a possible cause of low pregnancy rates in women of advanced maternal age undergoing in vitro fertilization (IVF) may be due to increased prevalence of chromosomal abnormalities, the use of preimplantation genetic screening had become increasingly more common at the time of this study, particularly in women of advanced maternal age. ¹³⁷⁻¹³⁹ However, this multicenter, double-blind randomized controlled trial comparing IVF with and without preimplantation genetic screening found that screening significantly reduced rates of ongoing pregnancies and live births after IVF in women of advanced maternal age.
90	A Multicenter, Randomized Controlled Trial of Dexamethasone for Bronchiolitis	7/26/07	While corticosteroids were commonly used at the time of this study to treat bronchiolitis in children, evidence on the effectiveness of this treatment modality was limited and results of prior studies had been mixed. ¹⁴⁰⁻¹⁴⁵ This randomized controlled trial showed that a single dose of oral dexamethasone administered in the emergency room did not significantly reduce the rate of hospital admission, the respiratory status after four hours, or later outcomes in children with moderate-to-severe bronchiolitis.
91	Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury	8/30/07	At the time of this study, no consensus had been reached for the best choice of fluids for fluid resuscitation in patients with traumatic brain injury. As a result, both fluid resuscitation with albumin or saline was advocated. ^{146, 147} A prior study comparing these two methods of fluid resuscitation in patients in the intensive care unit showed no

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			<p>significant difference between the two, but there was an increased number of deaths among patients with traumatic brain injury who received albumin.¹⁴⁸ This study was a follow-up study in this subgroup of patients and showed that fluid resuscitation with albumin in patients with traumatic brain injury was associated with higher mortality rates than resuscitation with saline.</p>
92	High-Dose Melphalan versus Melphalan plus Dexamethasone for AL Amyloidosis	9/13/07	<p>At the time of this study, high-dose melphalan with autologous hematopoietic stem-cell rescue was commonly used to treat patients with AL amyloidosis but transplant-related mortality was high.¹⁴⁹⁻¹⁵¹ This randomized trial showed that AL amyloidosis treatment with high-dose melphalan plus autologous hematopoietic stem-cell transplant was not superior to the outcome with standard-dose melphalan plus dexamethasone.</p>
93	Outcomes at 2 Years of Age after Repeat Doses of Antenatal Corticosteroids	9/20/07	<p>While a single dose of antenatal corticosteroids given to women at risk for preterm delivery reduces the risk of neonatal morbidity and mortality as well as long-term neurologic sequelae, infants born more than 7 days after the dose of antenatal corticosteroids had been shown to have lower birth weight and increased perinatal mortality compared to unexposed infants.^{152, 153} As a result, common practice was to repeat the dose of antenatal corticosteroids after 7 or more days even though there was no strong evidence to support the benefit of this practice.¹⁵⁴ The 2-year results of this randomized controlled trial comparing a single dose of antenatal steroids to repeated doses of antenatal steroids in women at risk for preterm delivery showed that even though repeated doses of antenatal steroid reduced neonatal morbidity, they did not change survival free of major neurosensory disability or body size at 2 years of age.</p>
94	Long-Term Outcomes after Repeat Doses of Antenatal Corticosteroids	9/20/07	<p>While evidence clearly supported the benefits of a single dose of corticosteroids on reducing perinatal morbidity and mortality, the optimal benefit of antenatal corticosteroid therapy lasted for 7 days.¹⁵⁵ Even though the risks and benefits of repeated doses of antenatal corticosteroids beyond 7 days in women who continued to be at risk for preterm delivery were unknown, this became common practice in the United States, the United Kingdom, and Australia.^{154, 156} The results of this randomized controlled trial showed that women who had been exposed to repeated doses of corticosteroids did not differ significantly in physical or neurocognitive measures as compared to children exposed to a single dose of antenatal corticosteroids. Additionally, there was a trend toward higher rates of cerebral palsy in children</p>

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			who had been exposed to repeat doses of corticosteroids.
95	Early Treatment with Prednisolone or Acyclovir in Bell's Palsy	10/18/07	Both prednisolone and acyclovir were commonly used, both alone and in combination for treatment of Bell's palsy; however, the evidence for the effectiveness of either of these treatments was lacking. ^{157, 158} This randomized, controlled trial showed that while early treatment with prednisolone significantly improved the chances of complete recovery at 3 and 9 months, there was no evidence of a benefit of acyclovir as monotherapy or as an adjunct to prednisolone.
96	Lung Transplantation and Survival in Children with Cystic Fibrosis	11/22/07	While lung transplantation was the most aggressive therapy for end-stage lung disease and cystic fibrosis was the most common indication for children, the benefits on patients' quality of life was uncertain. ¹⁵⁹ Also, transplantation accounted for a high percentage of deaths among cystic fibrosis patients. ¹⁶⁰ This large retrospective study showed that lung transplantation clearly improved survival in less than one percent of patients with cystic fibrosis and that prolongation of life by means of lung transplantation should not be expected in children with cystic fibrosis.
97	Rosuvastatin in Older Patients with Systolic Heart Failure	11/29/07	While there was some concern about the safety of statins in heart failure patients particularly related to skeletal and cardiac myopathy, multiple trials suggested that the use of statins was associated with better outcomes in heart failure patients, including better effects on left ventricular function and clinical status. ¹⁶¹⁻¹⁶⁷ This randomized controlled trial showed that rosuvastatin did not reduce the rate of death from cardiovascular causes or death from any cause in patients with systolic heart failure although it did reduce the number of cardiovascular hospitalizations. The drug did not increase rates of muscle-related or other adverse events.
98	Dexamethasone in Vietnamese Adolescents and Adults with Bacterial Meningitis	12/13/07	While corticosteroids were commonly used in the treatment of bacterial meningitis, evidence was mixed as to whether or not this treatment could reduce mortality rates and the risk of severe neurologic sequelae in adults, particularly in different settings outside of Europe. ¹⁶⁸⁻¹⁷¹ This randomized control trial showed that dexamethasone did not significantly improve outcomes in Vietnamese adolescents and adults with bacterial meningitis. There may be some beneficial effect for patients with biologically proven disease, including those who had previously received antibiotic treatment.
99	Corticosteroids for Bacterial Meningitis in Adults in Sub-	12/13/07	Because the host inflammatory response contributes significantly to neuronal injury in bacterial meningitis, corticosteroids had been

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	Saharan Africa		incorporated into treatment guidelines as adjuvant therapy. ¹⁷²⁻¹⁷⁵ However, data on the use of corticosteroids for bacterial meningitis in developing countries or areas of high HIV prevalence was limited. This randomized control trial in Malawi showed that dexamethasone for bacterial meningitis in an area with a high prevalence of HIV did not reduce mortality or morbidity.
100	Hydrocortisone Therapy for Patients with Septic Shock	1/10/08	Corticosteroids were widely used in patients with septic shock although their use was controversial ¹⁷⁶ . Of note, low doses of long duration showed a survival benefit ^{177, 178} , and steroids were endorsed by clinical guidelines ¹⁷⁹ . The Corticosteroid Therapy of Septic Shock (CORTICUS) study failed to show a mortality benefit in those patients with septic shock.
101	Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis	1/10/08	Aggressive blood glucose control was a widely accepted practice based on data attained from cardiac surgical patients ¹⁸⁰ . This practice continued despite evidence that it may cause harm ¹⁸¹ . In the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study not only was no mortality benefit noted, the trial was stopped early because of severe hypoglycemic events leading to prolonged ICU stays.
102	Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death	2/21/08	The use of Trasylo1 (Bayer HealthCare) in cardiac surgery to reduce blood loss and maintain platelet function was shown to lead to increase risk of in-hospital death and higher 5-year mortality ^{182, 183} . Despite this, the manufacturer maintained a favorable risk-benefit profile for the drug given the available data while suspending worldwide marketing. A retrospective analysis was performed from the Premier Perspective Comparative Database showed no benefit above that of aminocaproic acid but did show increases in inpatient mortality with respect to aprotinin vs. aminocaproic acid.
103	The effect of Aprotinin on Outcome after Coronary-Artery Bypass Grafting	2/21/08	In a single center, retrospective, observational cohort study performed at Duke it was shown looking at 10,275 consecutive patients who had CABG there is an increase in both short term and long term mortality with the use of Aprotinin.
104	Vasopressin versus Norepinephrine Infusion in Patient with Septic Shock	2/28/08	Vasopression was thought to be a reasonable adjunct in patients with septic shock based on shock physiology ^{184, 185} . It was also thought that it would reduce the use of catecholamines ¹⁸⁶ . As such it was used widely. This randomized trial found no mortality benefit from the administration of vasopressin as compared with norepinephrine among patients treated with catecholamines for shock.

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105	Anesthesia Awareness and the Bispectral Index	3/13/08	Bispectral index monitors (BIS) is an important brain-function monitor for Anesthesiologists to prevent sensory perception during surgery ^{187, 188} . The FDA has approved this monitor. The B-Aware study showed an absolute risk reduction of anesthesia awareness ¹⁸⁹ . The B-Unaware trial did not result in lower rate of anesthesia awareness nor lower use of volatile anesthetic gas.
106	Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia	4/3/08	It is well known that lowering LDL significantly reduces cardiovascular events ^{190, 191} . This primary prevention strategy was only limited by the side effects seen with increasing doses of statins ¹⁹² . It was thought that adding a second agent, ezetimibe to statin therapy would further lower LDL, thereby further reducing cardiovascular events ^{193, 194} . In the ENHANCE trial, despite significant incremental lowering of LDL the primary end point of mean intima-media thickness of the carotid-artery wall was not reduced.
107	Metformin versus Insulin for the Treatment of Gestational Diabetes	5/8/08	Treatment gestational diabetes had consisted of lifestyle modification and insulin treatment as this was shown to improve prenatal outcomes ¹⁹⁵ . Oral metformin was thought to be favorable for treatment in gestational diabetes because it does not cause weight gain and not associated with hypoglycemia ¹⁹⁶ . Its use became controversial because of the question of adverse perinatal effects ¹⁹⁷ . When metformin was compared with insulin in an open labeled RCT, there was no significant increase in perinatal complications.
108	A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery	5/29/08	There were three antifibrinolytic agents used in cardiac surgery to minimize bleeding and reduce transfusion requirements ^{198, 199} . All of the drugs had been shown to reduce the need for blood transfusion compared with placebo ^{198, 200} . There was controversy surrounding which drug should be used and led to variation in clinical practice ²⁰¹ . In the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) it was shown that aprotinin led to increased risk of death as compared to those receiving tranexamic acid or aminocaproic acid.
109	Intensive Blood Glucose Control and Vascular Outcomes in Patient with Type 2 Diabetes	6/12/08	A target A1C of 7.0% or less was the guideline for most patients with diabetes ²⁰² . However data were inconsistent how glucose control played a role in vascular disease ^{203, 204} . In the Action in Diabetes and Vascular Disease (ADVANCE) trial, the effects of glucose control on major vascular outcomes were evaluated. There was no evidence of reduction in macrovascular events and intensive glucose control was associated with increased risk of severe hypoglycemia and increased rate of hospitalization.
110	Effects of Intensive	6/12/08	A target A1C of 7.0% or less was the guideline for

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	Glucose Lowering in Type 2 Diabetes		most patients with diabetes ²⁰² . The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that a HbA1c target of less than 7.0% sustained for 3.5 years increased mortality and did not significantly reduce major cardiovascular events compared to a more permissive goal.
111	Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure	6/19/08	Available evidence suggested that patients with atrial fibrillation have worse prognosis and an independent risk factor for death than those with sinus rhythm ^{205, 206} . Because of this, conversion to sinus rhythm and maintenance with antiarrhythmic drugs was regularly attempted ²⁰⁷ . The value in preventing atrial fibrillation in those with heart failure was not known ²⁰⁸ . The Atrial Fibrillation and Congestive Heart Failure trial showed rhythm-control did not reduce the rate of death from cardiovascular causes as compared with rate-control.
112	Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema	7/10/08	With the hope to avoid the complications of tracheal intubation, non-invasive ventilator strategies are often used to improve oxygenation, reduce work of breathing and increase cardiac output ²⁰⁹⁻²¹² . However, in this multicenter study, no difference in the effect on short-term mortality between standard O ₂ therapy and noninvasive ventilation was found.
113	A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee	9/11/08	Arthroscopic surgery is widely used for osteoarthritis of the knee even in the face of scant evidence of its efficacy ^{213, 214} . This failed to show a benefit of arthroscopic surgery for treatment of osteoarthritis of the knee as assessed by WOMAC scores.
114	Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon	12/4/08	Peginterferon and ribavirin is the mainstay of therapy for Hepatitis C ²¹⁵ . Treatment options for patients who failed this primary therapy were limited, but many physicians continue Hepatitis C treatment for these refractory patients ²¹⁶ . It was thought that any viral suppression would lead to clinically important endpoints ²¹⁷ . The Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial did not show a reduction in clinical outcomes or progression of fibrosis.
115	Oral Prednisolone for Preschool Children with Acute Virus-Induced Wheezing	1/22/09	Several sets of national guidelines recommend that oral corticosteroids be given to preschool aged children who present to a hospital with virus-induced wheezing ²¹⁸ . However, the data for steroid use in this population is unclear. This large randomized, double-blind, placebo-controlled trial found no benefit of steroids among preschool children presenting to the hospital with acute, mild-to-moderate virus-induced wheezing.
116	Quality of Life after Late Invasive	2/19/09	Late opening (3-28) days after myocardial infarction) of a completely occluded coronary

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	Therapy for Occluded Arteries		artery is a common practice, particularly in the United States ²¹⁹⁻²²¹ . Such late opening is thought to improve mortality, ventricular function, and quality of life. Previously, the Occluded Artery Trial (OAT), a large randomized study, found no benefit in major cardiovascular events for this therapy (see reversal #86, 2006). This study reexamined OAT with respect to economic and quality of life outcomes. Late opening of occluded infarct-related arteries provided a marginal advantage for physical function at 4 months that was not sustained for the 3 year trial duration. Late opening resulted in higher total medical costs and lower quality-adjusted life expectancy at 2 years.
117	Intensive versus Conventional Glucose Control in Critically Ill Patients	3/26/09	Tight glycemic control (81 to 108 mg per deciliter) has been widely recommended and practiced in intensive care units ^{222, 223} . The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial showed that tight control, as compared with conventional glucose control, increased the absolute risk of death at 90 days by 2.6 percentage points.
118	Mortality Results from a Randomized Prostate-Cancer Screening Trial	3/26/09	The mortality benefit of routine prostate cancer specific antigen (PSA) screening continues to be debated. This large, randomized trial failed to detect any mortality benefit of routine screening among American men.
119	Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis	4/2/09	Because of their significant cardiovascular risk, hemodialysis users are recommended to take statins according to clinical guidelines worldwide ²²⁴ . A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) found no benefit in the combined end point of myocardial infarction, stroke, or death from cardiovascular causes among these patients, despite significant improvements in LDL cholesterol.
120	Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma	4/9/09	Acid reflux is thought to exacerbate wheezing among asthmatic patients. Current guidelines recommend that patients with poorly controlled asthma, particularly those with nighttime symptoms, be tested for gastroesophageal reflux disease, even in the absence of heartburn symptoms. If detected, proton-pump inhibitors (PPI) are recommended in these patients ²²⁵ . This study found that, despite a substantial incidence of GERD in this population, the addition of a PPI did not confer benefit.
121	Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs	4/16/09	Several sets of consensus guidelines (the American Academy of Neurology the American College of Obstetricians and Gynecologists and the International League against Epilepsy ²²⁶ do not distinguish among antiepileptic drugs used

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			during pregnancy with respect to teratogenic risks. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study found that valproic acid, as compared with other commonly used drugs, was associated with poorer cognitive function at 3 years of age.
122	Early versus Delayed, Provisional Eptifibatide in Acute Coronary Syndromes	5/21/09	2007 guidelines from the American College of Cardiology and the American Heart Association ²²⁷ recommend that among patients with NSTEMI and high-risk features aspirin and either clopidogrel or a glycoprotein IIb/IIIa inhibitor be given before angiography (i.e., early therapy) (class I recommendation). This study, the EARLY ACS trial, showed that contrary to this recommendation, the early use of eptifibatide was not superior to eptifibatide post angiography, and likely resulted in higher rates of bleeding.
123	Endoscopic versus Open Vein-Graft Harvesting in Coronary-Artery Bypass Surgery	7/16/09	Endoscopic harvesting of the saphenous vein for coronary artery bypass surgery has swelled in popularity. It is a procedure which eliminates the need for the long incisions associated with open harvesting, reduces wound infections, decreases postoperative pain, and shortens length of stay in the hospital. In fact, in 2005 the International Society for Minimally Invasive Cardiothoracic Surgery recommended that it should replace open harvesting as standard of care ²²⁸ . This study showed that endoscopic harvesting resulted in higher rates of vein-graft failure at 12 to 18 months, and, at 3 years, higher rates of death, myocardial infarction, or repeat revascularization.
124	A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures	8/6/09	Vertebroplasty is a medical procedure where cement is injected into fractured spinal bone, in theory, restoring the original shape, diminishing pain, and stabilizing the fragments. Interventional neuroradiologists pioneered its use in the United States in the 1990s. By the late 1990s, case series were published, and technical details were shared. Proponents of vertebroplasty lobbied Medicare to fund the procedure, and in 2001, their request was granted. In that year, more than 14,000 vertebroplasties were performed in the United States, and by 2004, that number was 27,000 ²²⁹ . Vertebroplasty quickly became a multi-million dollar a year industry. In these paired articles, the procedure was shown to be no better than a sham procedure.
125	A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures	8/6/09	same as above
126	Weight Lifting in Women with Breast-Cancer-Related	8/13/09	Breast-cancer survivors with lymphedema may limit the use of the affected arm based upon guidance from the American Cancer Society ²³⁰ .

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	Lymphedema		This randomized trial showed, that contrary to this position, weight lifting improves the symptoms of lymphedema.
127	Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients	10/22/09	Renal failure is associated with substantial morbidity and mortality and is common among patients requiring intensive care. In recent years, there has been a widespread increase in the use of higher-intensity continuous renal-replacement therapy compared to lower intensity replacement therapy among critically ill patients ^{231, 232} . This large, multicenter, randomized, controlled trial of intensity of renal support in acute kidney injury (RENAL) indicates that such practice is not justified, as high intensity therapy did not improve mortality at 90 days
128	Revascularization versus Medical Therapy for Renal-Artery Stenosis	11/12/09	Renal artery stenosis is associated with hypertension and kidney disease, but it is unclear if the relationship is causal. Despite this uncertainty, data from studies in the United States indicate that revascularization is performed in 16% of patients with newly diagnosed atherosclerotic renovascular disease and hypertension ²³³ . This large randomized trial (ASTRAL) of revascularization with medical management versus medical management alone found substantial risks but no evidence of benefit from revascularization in this population.
129	A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease	11/19/09	The use of erythropoiesis stimulating agents among patients with anemia and chronic kidney disease is widespread. The belief that this therapy confers benefit is so strong that major clinical trials have considered the use of placebo unnecessary or even unethical ^{234, 235} . The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) showed that the use of these agents did not reduce the risk of either death or a cardiovascular event or a renal event and was associated with an increased risk of stroke.
130	Extended-Release Niacin or Ezetimibe and Carotid Intima-Media Thickness	11/26/09	Zetia or Ezetimibe was licensed by the Food and Drug Administration in 2002 based upon its ability to reduce the LDL cholesterol level without major short term side effects. Since that time, Zetia has been prescribed widely to improve cardiovascular risk. A number of other studies have suggested that the net effect of Zetia may not be beneficial. This current study shows that for one surrogate of atherosclerotic disease the Zetia does not result in the regression of carotid artery intimal medial thickness, while niacin (another cardiovascular drug) does. This study further undermines the purported benefit of Zetia with respect to cardiovascular risk.
131	Preoperative Biliary Drainage for Cancer	1/14/10	Jaundice in surgical patients is postulated to increase the rate of postoperative complications.

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	of the Head of the Pancreas		Many surgical centers have employed biliary drainage prior to surgical intervention for cancer of the head of the pancreas, but there is conflicting evidence regarding its effect on morbidity and mortality. ²³⁶⁻²⁴¹ This multicenter, randomized trial found that routine preoperative biliary drainage increases the rate of serious complications without a mortality benefit.
132	Outcomes after Internal versus External Tocodynamometry for Monitoring Labor	1/28/10	The Dutch Society of Obstetrics and Gynecology recommends the routine use internal tocodynamometry during all cases of induction or augmentation of labor. Likewise, the American College of Obstetrics and Gynecology advocates its use in numerous circumstances. However, these recommendations are grounded in expert opinion, and smaller trials have failed to demonstrate a net benefit with internal versus external tocodynamometry. ^{242, 243} In a multicenter, randomized trial, the authors found that internal tocodynamometry did not reduce the rate of operative deliveries, adverse neonatal outcomes, rates of use of analgesia or antibiotics, or time to delivery .
133	Comparison of Dopamine and Norepinephrine in the Treatment of Shock	3/4/10	Consensus guidelines recommend both dopamine and norepinephrine as first line agents in the treatment of patients with shock, and many physicians favor dopamine in cardiogenic shock. ²⁴⁴⁻²⁴⁶ The Sepsis Occurrence in Acutely Ill Patients (SOAP) study observationally showed that dopamine administration increased the risk of death in the intensive care unit. ²⁴⁷ This randomized study found that dopamine administration resulted in about twice as many arrhythmic events in the total cohort, while subgroup analysis demonstrated higher 28-day mortality rates in patients with cardiogenic shock.
134	Lenient versus Strict Rate Control in Patients with Atrial Fibrillation	4/15/10	The American Heart Association/American College of Cardiology/European Society of Cardiology guidelines recommend strict rate control (resting heart rate < 80 beats per minute and exercise heart rate < 110 beats per minute) to reduce morbidity and mortality from atrial fibrillation, based upon expert consensus. ²⁴⁸ This study found that lenient rate control (resting heart rate <110 beats per minute) was noninferior to strict rate control and much easier to achieve in patients with permanent atrial fibrillation.
135	Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus	4/29/10	Fibrate therapy has long been used in the treatment of dyslipidemia in type II diabetes. Though statins are considered primary therapy to reduce the risk of cardiovascular events, rates remain elevated despite use. Two large previous studies of fibrate therapy in type II diabetics conflicted with regard to their effect on

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			cardiovascular events. ^{249, 250} The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study demonstrated here that statin and fibrate combination therapy did not differ in outcomes compared with statin therapy alone at similar levels of serum lipids.
136	Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus	4/29/10	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended initiating blood pressure treatment in patients with diabetes who have systolic blood pressures of 130 mmHg or greater. ²⁵¹ This recommendation was based upon expert opinion, given the higher risk of diabetic patients for adverse cardiovascular events even at prehypertensive levels. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study tested whether targeting a systolic blood pressure below 120 mmHg in comparison to a target below 140 mmHg would reduce major cardiovascular events. The intensive-therapy group did not differ from the standard-therapy group with respect to the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Intensive treatment did lower the stroke risk in intensively treated patients, but the absolute risk reduction was 0.21% and also resulted in more adverse events related to therapy.
137	Aspirin plus Heparin or Aspirin Alone in Women with Recurrent Miscarriage	4/29/10	The pathogenesis of women with unexplained, recurrent miscarriage may be similar to those with antiphospholipid antibody syndrome, who are generally treated with antiplatelet and anticoagulation therapy during pregnancy. Limited studies in women with unexplained, recurrent miscarriage have shown a benefit of aspirin plus low-molecular-weight heparin. ²⁵²⁻²⁵⁴ However, this large, multicenter study which randomized women with unexplained, recurrent miscarriage to aspirin plus heparin, aspirin alone, or placebo failed to demonstrate a benefit in live-birth rate with aspirin plus heparin or aspirin alone.
138	Quality Indicators for Colonoscopy and the Risk of Interval Cancer	5/13/10	Professional societies have advocated cecal intubation as a quality-indicator for colonoscopy without previous validation of the measure. ^{255, 256} However, this large, retrospective study failed to demonstrate cecal intubation as a predictor of interval colon cancer.
139	Long-Term Outcome of Open or Endovascular Repair of Abdominal Aortic Aneurysm	5/20/10	Endovascular repair improves perioperative survival over conventional open repair of abdominal aortic aneurysms. However, the benefit does not last beyond the second post-op year in two year follow-up studies, and long term data on morbidity and mortality are lacking. ²⁵⁷⁻²⁶⁰ After a

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			<p>median follow-up of 6.4 years, this randomized, controlled trial showed similar survival rates but higher reintervention rates for endovascular repair, due to reduced endograft durability.</p>
140	A Randomized Trial of Treatment for Acute Anterior Cruciate Ligament Tears	7/22/10	<p>Reconstruction for acute anterior cruciate ligament (ACL) tears is a common and expensive treatment option, while structured rehabilitation is less frequently offered. However, there is insufficient evidence from randomized trials to inform current practice.^{261, 262} This trial randomized young, active adults to structured rehabilitation plus early ACL reconstructive surgery or structured rehabilitation with delayed ACL reconstruction. The authors found no advantage of routine early surgical reconstruction as measured by change in the Knee Injury and Osteoarthritis Outcome Score (KOOS₄), indicating that more than half of all surgical reconstructions can be reasonably avoided. Although 23/59 patients in the latter group eventually opted for surgery, the results were similar when accounting for treatment actually received.</p>
141	CPR with Chest Compression Alone or with Rescue Breathing	7/29/10	<p>Nearly a half century after chest compression and rescue breathing were proposed as routine cardiopulmonary resuscitation (CPR)²⁶³ have the most fundamental assumptions been questioned. Two randomized trials in this issue both show no benefit from rescue breathing when added to chest only compression. The results of these studies have fueled greater skepticism, and some editorialists have called for trials to test whether any CPR is better than a still lesser strategy of automated external defibrillator alone²⁶⁴.</p>
142	Compression-Only CPR or Standard CPR in Out-of-Hospital Cardiac Arrest	7/29/10	<p>Same as above</p>
143	Suicide-Related Events in Patients Treated with Antiepileptic Drugs	8/5/10	<p>The Food and Drug Administration issued a safety warning in January 2008 on the risk of suicidality associated with anti-epileptic drugs based upon the results of a meta-analysis that showed a two-fold increased risk of suicidality (defined as suicidal ideation or behavior). However, this assessment was limited by a lack of standardized definition of suicidality among the pooled trials. The authors here examined the association of anti-epileptic drugs and suicide-related events (attempted or completed suicides) in a case-control analysis, stratifying by clinical comorbidities. Treatment with anti-epileptic drugs did not increase the risk of suicide-related events in patients with epilepsy but did increase the risk</p>

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			among patients with depression and among those without epilepsy, depression, or bipolar disorder.
144	A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis	8/12/10	Clinical practice guidelines from 1997 have recommended early initiation of dialysis based upon nonrandomized data suggesting improved survival and quality of life. ²⁶⁵ However, since that time, observational data have suggested a net harm with early initiation. ²⁶⁶⁻²⁶⁸ This study showed that early initiation of dialysis (estimated glomerular filtration rate [GFR] between 10.0 to 14.0 ml per minute per 1.73 m ² of body-surface area) did not improve survival or clinical outcomes when compared with the late-start group (estimated GFR 5.0-7.0 ml per minute per 1.73 m ² of body-surface area).
145	Gentamicin–Collagen Sponge for Infection Prophylaxis in Colorectal Surgery	9/9/10	The gentamicin-collagen sponge has been approved for use in numerous countries and used in millions of patients worldwide since 1985. A single-center, randomized trial showed a 70% decrease in surgical-site infection with implantation of the sponge. ²⁶⁹ This large, multicenter, phase 3 trial however showed that gentamicin-collagen sponge paradoxically resulted in significantly more surgical-site infections, was associated with more visits to the emergency room or surgical office, and more frequently precipitated rehospitalization for the infection.
146	Effects of CYP2C19 Genotype on Outcomes of Clopidogrel Treatment	10/28/10	The <i>CYP2C19</i> gene is involved in the conversion of clopidogrel to its active metabolite, and patients with certain genetic variants (“poor metabolizers”) have been shown to be at higher risk for recurrent cardiovascular events. The Food and Drug Administration issued a black-box warning regarding the reduced efficacy of clopidogrel in patients who are carriers of two loss-of-function alleles in the <i>CYP2C19</i> gene. However, this statement was based upon observational data from only clopidogrel-treated patients and did not include data from large, randomized controlled trials to reduce the possibility of confounding. ²⁷⁰⁻²⁷² The authors of the present study pooled data from two large, randomized controlled trials, and showed that among patients with acute coronary syndromes or atrial fibrillation, the safety and efficacy of clopidogrel compared with placebo are consistent, regardless of <i>CYP2C19</i> loss-of-function carrier status.

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