

Teaching papers- Therapy

Miller, E. R., 3rd, R. Pastor-Barriuso, et al. (2005). "**Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality.**" *Ann Intern Med* **142**(1): 37-46.

Type of Question: Therapy **Intermediate Meta analysis.**

Teaching Notes: Solid methodology; Recent, pertinent to many disciplines; Good Discussion Points: Nice illustration of how meta-analysis is used to detect important, but rare adverse events occurring in clinical trials. Results are clearly laid out including data table, forest plots, dose-effect curve; Good paper to discuss confidence intervals (Figures 2 and 4 on pages 42 and 44). The length of the paper may intimidate some earlier learners

Abstract: **BACKGROUND:** Experimental models and observational studies suggest that vitamin E supplementation may prevent cardiovascular disease and cancer. However, several trials of high-dosage vitamin E supplementation showed non-statistically significant increases in total mortality. **PURPOSE:** To perform a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality by using data from randomized, controlled trials. **PATIENTS:** 135,967 participants in 19 clinical trials. Of these trials, 9 tested vitamin E alone and 10 tested vitamin E combined with other vitamins or minerals. The dosages of vitamin E ranged from 16.5 to 2000 IU/d (median, 400 IU/d). **DATA SOURCES:** PubMed search from 1966 through August 2004, complemented by a search of the Cochrane Clinical Trials Database and review of citations of published reviews and meta-analyses. No language restrictions were applied. **DATA EXTRACTION:** 3 investigators independently abstracted study reports. The investigators of the original publications were contacted if required information was not available. **DATA SYNTHESIS:** 9 of 11 trials testing high-dosage vitamin E ($>$ or $=400$ IU/d) showed increased risk (risk difference > 0) for all-cause mortality in comparisons of vitamin E versus control. The pooled all-cause mortality risk difference in high-dosage vitamin E trials was 39 per 10,000 persons (95% CI, 3 to 74 per 10,000 persons; $P = 0.035$). For low-dosage vitamin E trials, the risk difference was -16 per 10,000 persons (CI, -41 to 10 per 10,000 persons; $P > 0.2$). A dose-response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d. **LIMITATIONS:** High-dosage ($>$ or $=400$ IU/d) trials were often small and were performed in patients with chronic diseases. The generalizability of the findings to healthy adults is uncertain. Precise estimation of the threshold at which risk increases is difficult. **CONCLUSION:** High-dosage ($>$ or $=400$ IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.

Taylor, A. L., S. Ziesche, et al. (2004). "**Combination of isosorbide dinitrate and hydralazine in blacks with heart failure.**" *N Engl J Med* **351**(20): 2049-2057.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Also referred to as the A-HEFT Trial (African American Heart Failure Trial), this is an RCT of isosorbide / hydralazine in participants who self-identified as black (defined as of African Descent). ACP Journal Club Summary 2005; 142 (2): 37. Good discussion points: Controversial motivation: NitroMed, the company that holds the patent on the fixed dose combination drug, sponsored the trial. This raises some ethical questions about the motivation for performing the trial in a single racial group as a mechanism to obtain more rapid approval from the FDA (see NEJM Perspective that accompanied the article when it was published. NEJM 2004; 351:2035-37) Controversial recommendations: Should one make race-based recommendations, given proven efficacy in self-identified Blacks and lack of published efficacy in Caucasians? Straightforward Therapy calculations: Can easily calculate NNT for All-cause mortality and for first hospitalization for CHF. Can discuss the concept of Composite Score. Why would the authors have planned the analysis that way? This might lead to a general discussion of the pros and cons of combined outcomes.

Abstract: **BACKGROUND:** We examined whether a fixed dose of both isosorbide dinitrate and hydralazine provides additional benefit in blacks with advanced heart failure, a subgroup previously noted to have a favorable response to this therapy. **METHODS:** A total of 1050 black patients who had New York Heart Association class III or IV heart failure with dilated ventricles were randomly assigned to receive a fixed dose of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for

heart failure. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and change in the quality of life. **RESULTS:** The study was terminated early owing to a significantly higher mortality rate in the placebo group than in the group given isosorbide dinitrate plus hydralazine (10.2 percent vs. 6.2 percent, $P=0.02$). The mean primary composite score was significantly better in the group given isosorbide dinitrate plus hydralazine than in the placebo group (-0.1 ± 1.9 vs. -0.5 ± 2.0 , $P=0.01$; range of possible values, -6 to $+2$), as were its individual components (43 percent reduction in the rate of death from any cause [hazard ratio, 0.57; $P=0.01$] 33 percent relative reduction in the rate of first hospitalization for heart failure [16.4 percent vs. 22.4 percent, $P=0.001$], and an improvement in the quality of life [change in score, -5.6 ± 20.6 vs. -2.7 ± 21.2 , with lower scores indicating better quality of life; $P=0.02$; range of possible values, 0 to 105]). **CONCLUSIONS:** The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure including neurohormonal blockers is efficacious and increases survival among black patients with advanced heart failure.

March, J., S. Silva, et al. (2004). "**Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial.**" *Jama* 292(7): 807-820.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: This Multicenter RCT is a landmark trial in adolescents as the first large trial to compare placebo to cognitive behavior +/- antidepressant medication (Fluoxetine) in this age group. Strong, clearly reported methods; Evidence-based Mental Health Summary 2005; 8: 10; Possible Discussion Points: The trial is also notable for a timely publication given that in February 2004 the FDA convened an advisory panel to review possible increased risk of suicidality in patients on SSRI medications. There was intense media spotlight associated with the FDA black box warning describing potential increase risk of suicidal thoughts and behaviors in children and adolescents. (See related article in table: Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression; nested case-control study, Harm)

Abstract: **CONTEXT:** Initial treatment of major depressive disorder in adolescents may include cognitive-behavioral therapy (CBT) or a selective serotonin reuptake inhibitor (SSRI). However, little is known about their relative or combined effectiveness. **OBJECTIVE:** To evaluate the effectiveness of 4 treatments among adolescents with major depressive disorder. **DESIGN, SETTING, AND PARTICIPANTS:** Randomized controlled trial of a volunteer sample of 439 patients between the ages of 12 to 17 years with a primary Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnosis of major depressive disorder. The trial was conducted at 13 US academic and community clinics between spring 2000 and summer 2003. **INTERVENTIONS:** Twelve weeks of (1) fluoxetine alone (10 to 40 mg/d), (2) CBT alone, (3) CBT with fluoxetine (10 to 40 mg/d), or (4) placebo (equivalent to 10 to 40 mg/d). Placebo and fluoxetine alone were administered double-blind; CBT alone and CBT with fluoxetine were administered unblinded. **MAIN OUTCOME MEASURES:** Children's Depression Rating Scale-Revised total score and, for responder analysis, a (dichotomized) Clinical Global Impressions improvement score. **RESULTS:** Compared with placebo, the combination of fluoxetine with CBT was statistically significant ($P=.001$) on the Children's Depression Rating Scale-Revised. Compared with fluoxetine alone ($P=.02$) and CBT alone ($P=.01$), treatment of fluoxetine with CBT was superior. Fluoxetine alone is a superior treatment to CBT alone ($P=.01$). Rates of response for fluoxetine with CBT were 71.0% (95% confidence interval [CI], 62%-80%); fluoxetine alone, 60.6% (95% CI, 51%-70%); CBT alone, 43.2% (95% CI, 34%-52%); and placebo, 34.8% (95% CI, 26%-44%). On the Clinical Global Impressions improvement responder analysis, the 2 fluoxetine-containing conditions were statistically superior to CBT and to placebo. Clinically significant suicidal thinking, which was present in 29% of the sample at baseline, improved significantly in all 4 treatment groups. Fluoxetine with CBT showed the greatest reduction ($P=.02$). Seven (1.6%) of 439 patients attempted suicide; there were no completed suicides. **CONCLUSION:** The combination of fluoxetine with CBT offered the most favorable tradeoff between benefit and risk for adolescents with major depressive disorder.

Annane, D., E. Bellissant, et al. (2004). "**Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis.**" *Bmj* 329(7464): 480.

Type of Question: Therapy **Intermediate / Advanced Meta analysis.**

Teaching Notes: This is a well-done meta-analysis that can allow discussion of important concepts for intermediate to advanced learners who want to push their understanding of meta-analysis. ACP Journal Club Summary 2005; 142 (2): 30. Good discussion points: Can discuss both quasi-randomization (definition: pseudo random allocation method such as day of birth, order of participant enrollment in study, day of the week, medical record number etc.) and the introduction of possible selection bias. Can refer readers to tables 3 and 4 where specific design issues are identified. Can also discuss heterogeneity and the authors' attempts to explain it as multifactorial, including differences in methodologic strength and dose/ duration of intervention. Excellent review of how to think about subgroup analysis. Possible strengths (pre-stated hypothesis, statistically significant effect), and pitfalls (difference is comparisons between studies rather than within studies) of the interpretation of this subgroup analysis.

Abstract: **OBJECTIVE:** To assess the effects of corticosteroids on mortality in patients with severe sepsis and septic shock. **DATA SOURCES:** Randomised and quasi-randomised trials of corticosteroids versus placebo (or supportive treatment alone) retrieved from the Cochrane infectious diseases group's trials register, the Cochrane central register of controlled trials, Medline, Embase, and LILACS. **REVIEW METHOD:** Two pairs of reviewers agreed on eligibility of trials. One reviewer entered data on to the computer and four reviewers checked them. We obtained some missing data from authors of trials and assessed methodological quality of trials. **RESULTS:** 16/23 trials (n = 2063) were selected. Corticosteroids did not change 28 day mortality (15 trials, n = 2022; relative risk 0.92, 95% confidence interval 0.75 to 1.14) or hospital mortality (13 trials, n = 1418; 0.89, 0.71 to 1.11). There was significant heterogeneity. Subgroup analysis on long courses (> or = 5 days) with low dose (< or = 300 mg hydrocortisone or equivalent) corticosteroids showed no more heterogeneity. The relative risk for mortality was 0.80 at 28 days (five trials, n = 465; 0.67 to 0.95) and 0.83 at hospital discharge (five trials, n = 465, 0.71 to 0.97). Use of corticosteroids reduced mortality in intensive care units (four trials, n = 425, 0.83, 0.70 to 0.97), increased shock reversal at 7 days (four trials, n = 425; 1.60, 1.27 to 2.03) and 28 days (four trials, n = 425, 1.26, 1.04 to 1.52) without inducing side effects. **CONCLUSIONS:** For all trials, regardless of duration of treatment and dose, use of corticosteroids did not significantly affect mortality. With long courses of low doses of corticosteroids, however, mortality at 28 days and hospital mortality was reduced.

Larson, E. L., S. X. Lin, et al. (2004). "Effect of antibacterial home cleaning and handwashing products on infectious disease symptoms: a randomized, double-blind trial." Ann Intern Med 140(5): 321-329.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Fun paper that looked at the effect of antibacterial home cleaning and handwashing products in households with at least one pre-school age child. Fun topic for anyone who has or works with small children (or has to clean their home...) Good discussion points: Nice opportunity to discuss randomization methods looking at the use of antibacterial products as the intervention. Problem with teaching this paper: It is an equivalency trial, therefore you cannot calculate risk reduction or number needed to treat. You can use this as an opportunity to discuss p-values and confidence intervals that are NOT significant.

Abstract: **BACKGROUND:** Despite the widespread household use of cleaning and personal hygiene products containing antibacterial ingredients, their effects on the incidence of infectious disease symptoms have not been studied. **OBJECTIVE:** To evaluate the effect of antibacterial cleaning and handwashing products for consumers on the occurrence of infectious disease symptoms in households. **DESIGN:** Randomized, double-blind clinical trial. **SETTING:** Northern Manhattan inner-city neighborhood, New York. **PARTICIPANTS:** 238 primarily Hispanic households (1178 persons) that included at least one preschool-age child. **Interventions:** Households were randomly assigned to use either antibacterial or nonantibacterial products for general cleaning, laundry, and handwashing. All products were commercially available, but the packaging was blinded and the products were provided free to participants. **MEASUREMENTS:** Hygiene practices and infectious disease symptoms were monitored by weekly telephone calls, monthly home visits, and quarterly interviews for 48 weeks. **RESULTS:** Symptoms were primarily respiratory: During 26.2% (717 of 2736) of household-months, 23.3% (640 of 2737) of household-months, and 10.2% (278 of 2737) of household-months, one or more members of the household had a runny nose, cough, or sore throat, respectively. Fever was present during 11% (301 of

2737) of household-months, vomiting was present in 2.2% (61 of 2737), diarrhea was present in 2.5% (69 of 2737), and boils or conjunctivitis were present in 0.77% (21 of 2737). Differences between intervention and control groups were not significant for any symptoms (all unadjusted and adjusted relative risks included 1.0) or for numbers of symptoms (overall incidence density ratio, 0.96 [95% CI, 0.82 to 1.12]). **CONCLUSIONS:** The tested antibacterial products did not reduce the risk for symptoms of viral infectious diseases in households that included essentially healthy persons. This does not preclude the potential contribution of these products to reducing symptoms of bacterial diseases in the home.

Ross, J. R., Y. Saunders, et al. (2003). "**Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer.**" *Bmj* 327(7413): 469.

Type of Question: Therapy **Intermediate / Advanced Meta analysis.**

Teaching Notes: Strong methodology Meta-analysis with very clear description of methods (Figure 1 nice overview for flow of selected papers with on-line access to even more complete details). Good Discussion Points: Lots of great forest plots! / Both endpoints that use straight RR and those needing conversion to effect size / No data table in paper, but available from a website. Generates great discussion about homogeneity and generalizability (includes lytic cancers, blastic cancers, wide population and age range). Good paper to point out pitfall of trying to get a systematic review to answer more than its focused clinical question (e.g., which bisphosphonate should you try first?)

Abstract: **OBJECTIVE:** To review the evidence for the use of bisphosphonates to reduce skeletal morbidity in cancer patients with bone metastases. **DATA SOURCES:** Electronic databases, scanning reference lists, and consultation with experts and pharmaceutical companies. Foreign language papers were included. **STUDY SELECTION:** Included trials were randomised controlled trials of patients with malignant disease and bone metastases who were treated with oral or intravenous bisphosphonate compared with another bisphosphonate, placebo, or standard care. All trials measured at least one outcome of skeletal morbidity. **RESULTS:** 95 articles were identified; 30 studies fulfilled inclusion criteria. In studies that lasted \geq 6 months, compared with placebo bisphosphonates significantly reduced the odds ratio for fractures (vertebral 0.69, 95% confidence interval 0.57 to 0.84, $P < 0.0001$; non-vertebral 0.65, 0.54 to 0.79, $P < 0.0001$; combined 0.65, 0.55 to 0.78, $P < 0.0001$), radiotherapy (0.67, 0.57 to 0.79, $P < 0.0001$), and hypercalcaemia (0.54, 0.36 to 0.81, $P = 0.003$) but not for orthopaedic surgery (0.70, 0.46 to 1.05, $P = 0.086$) or spinal cord compression (0.71, 0.47 to 1.08, $P = 0.113$). The reduction in orthopaedic surgery was significant in studies that lasted over a year (0.59, 0.39 to 0.88, $P = 0.009$). Use of bisphosphonates significantly increased time to first skeletal related event but did not increase survival. Subanalyses showed that most evidence supports use of intravenous aminobisphosphonates. **CONCLUSIONS:** In people with metastatic bone disease bisphosphonates significantly decrease skeletal morbidity, except for spinal cord compression and increased time to first skeletal related event. Treatment should start when bone metastases are diagnosed and continue until it is no longer clinically relevant.

(2002). "**Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).**" *Jama* 288(23): 2981-2997.

Type of Question: Therapy **Very Advanced RCT.**

Teaching Notes: This is an example of a very complicated paper with multiple arms, multiple outcomes and what feels like a zillion tables and graphs. However, it is also an example of a paper that had a great impact on internal medicine practice; Think of how you would approach this paper in a way that would not be intimidating, either as a practitioner who wants to understand the evidence in order to best apply it, or as an educator who would like to summarize the most important points so the importance of this study can be appreciated. **Warning:** This paper is not for the faint at heart and the program is not responsible for any unintended harms that may come from reading this paper.

Abstract: **CONTEXT:** Antihypertensive therapy is well established to reduce hypertension-related morbidity and mortality, but the optimal first-step therapy is unknown. **OBJECTIVE:** To determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs treatment with a diuretic. **DESIGN:** The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, active-controlled clinical trial conducted from February 1994

through March 2002. **SETTING AND PARTICIPANTS:** A total of 33 357 participants aged 55 years or older with hypertension and at least 1 other CHD risk factor from 623 North American centers. **INTERVENTIONS:** Participants were randomly assigned to receive chlorthalidone, 12.5 to 25 mg/d (n = 15 255); amlodipine, 2.5 to 10 mg/d (n = 9048); or lisinopril, 10 to 40 mg/d (n = 9054) for planned follow-up of approximately 4 to 8 years. **MAIN OUTCOME MEASURES:** The primary outcome was combined fatal CHD or nonfatal myocardial infarction, analyzed by intent-to-treat. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure [HF], and peripheral arterial disease). **RESULTS:** Mean follow-up was 4.9 years. The primary outcome occurred in 2956 participants, with no difference between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% CI, 0.90-1.07) for amlodipine (6-year rate, 11.3%) and 0.99 (95% CI, 0.91-1.08) for lisinopril (6-year rate, 11.4%). Likewise, all-cause mortality did not differ between groups. Five-year systolic blood pressures were significantly higher in the amlodipine (0.8 mm Hg, P = .03) and lisinopril (2 mm Hg, P < .001) groups compared with chlorthalidone, and 5-year diastolic blood pressure was significantly lower with amlodipine (0.8 mm Hg, P < .001). For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% vs 7.7%; RR, 1.38; 95% CI, 1.25-1.52). For lisinopril vs chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs 30.9%; RR, 1.10; 95% CI, 1.05-1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 1.02-1.30); and HF (8.7% vs 7.7%; RR, 1.19; 95% CI, 1.07-1.31). **CONCLUSION:** Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.

Van Gelder, I. C., V. E. Hagens, et al. (2002). **"A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation."** *N Engl J Med* 347(23): 1834-1840.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Straightforward RCT with clear methods and clear results reporting. Good Kaplan-Meier curves. Good easy numbers for calculation of number needed to treat (see table 2 which reports absolute risk differences). Also can use same table for discussion of confidence intervals and statistical significance. Good discussion points: Great data for discussion of primary vs. secondary end points and composite end points. Can be used to discuss the differences between non-inferiority / equivalence / superiority and considerations of sample size.

Abstract: **BACKGROUND:** Maintenance of sinus rhythm is the main therapeutic goal in patients with atrial fibrillation. However, recurrences of atrial fibrillation and side effects of antiarrhythmic drugs offset the benefits of sinus rhythm. We hypothesized that ventricular rate control is not inferior to the maintenance of sinus rhythm for the treatment of atrial fibrillation. **METHODS:** We randomly assigned 522 patients who had persistent atrial fibrillation after a previous electrical cardioversion to receive treatment aimed at rate control or rhythm control. Patients in the rate-control group received oral anticoagulant drugs and rate-slowing medication. Patients in the rhythm-control group underwent serial cardioversions and received antiarrhythmic drugs and oral anticoagulant drugs. The end point was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs. **RESULTS:** After a mean (+/-SD) of 2.3+/-0.6 years, 39 percent of the 266 patients in the rhythm-control group had sinus rhythm, as compared with 10 percent of the 256 patients in the rate-control group. The primary end point occurred in 44 patients (17.2 percent) in the rate-control group and in 60 (22.6 percent) in the rhythm-control group. The 90 percent (two-sided) upper boundary of the absolute difference in the primary end point was 0.4 percent (the prespecified criterion for noninferiority was 10 percent or less). The distribution of the various components of the primary end point was similar in the rate-control and rhythm-control groups. **CONCLUSIONS:** Rate control is not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes and may be appropriate therapy in patients with a recurrence of persistent atrial fibrillation after electrical cardioversion.

Shepherd, J., G. J. Blauw, et al. (2002). **"Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial."** *Lancet* 360(9346): 1623-1630.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Excellent randomized controlled trial methodology applicable to the elderly. Has an ACP journal club summary of the paper and results, which can be used for teaching. Nice Hazard plots are a good way to demonstrate effect size and confidence intervals. Good discussion points: Fantastic discussion paper for the difference between validity and applicability. Outstanding methods that show a treatment effect in this older population. However the decision making process for whether one would want to treat someone who was 80 years old and had risk factors but no known CAD is quite another story... Fun teaching exercise is to have several different case-patients with different characteristics and values. Have the trainees apply the same evidence to different patients. Can discuss the balance of benefits of therapy vs. potential harms and costs both to individual patients and to society.

Abstract: **BACKGROUND:** Although statins reduce coronary and cerebrovascular morbidity and mortality in middle-aged individuals, their efficacy and safety in elderly people is not fully established. Our aim was to test the benefits of pravastatin treatment in an elderly cohort of men and women with, or at high risk of developing, cardiovascular disease and stroke. **METHODS:** We did a randomised controlled trial in which we assigned 5804 men (n=2804) and women (n=3000) aged 70-82 years with a history of, or risk factors for, vascular disease to pravastatin (40 mg per day; n=2891) or placebo (n=2913). Baseline cholesterol concentrations ranged from 4.0 mmol/L to 9.0 mmol/L. Follow-up was 3.2 years on average and our primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. Analysis was by intention-to-treat. **FINDINGS:** Pravastatin lowered LDL cholesterol concentrations by 34% and reduced the incidence of the primary endpoint to 408 events compared with 473 on placebo (hazard ratio 0.85, 95% CI 0.74-0.97, p=0.014). Coronary heart disease death and non-fatal myocardial infarction risk was also reduced (0.81, 0.69-0.94, p=0.006). Stroke risk was unaffected (1.03, 0.81-1.31, p=0.8), but the hazard ratio for transient ischaemic attack was 0.75 (0.55-1.00, p=0.051). New cancer diagnoses were more frequent on pravastatin than on placebo (1.25, 1.04-1.51, p=0.020). However, incorporation of this finding in a meta-analysis of all pravastatin and all statin trials showed no overall increase in risk. Mortality from coronary disease fell by 24% (p=0.043) in the pravastatin group. Pravastatin had no significant effect on cognitive function or disability. **INTERPRETATION:** Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals. PROSPER therefore extends to elderly individuals the treatment strategy currently used in middle aged people.

Hull, R. D., G. F. Pineo, et al. (2001). "Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review." *Ann Intern Med* 135(10): 858-869.

Type of Question: Therapy **Intermediate Meta analysis.**

Teaching Notes: Important question which prompts good discussion of risks v. benefits v. cost. Good Discussion Points: Strengths: Well designed with clear description of methods. Can use methods to prompt vocabulary discussion for concepts pertaining to Meta-analysis (e.g. methods for validity assessment, summary treatment effects, sensitivity analysis, heterogeneity); Weaknesses: Variety of interventions can become very confusing to learners. More Advanced Discussion: might consider getting the QUOROM statement that is referenced in the methods of the paper (p. 859) for more in depth discussion of Meta-analysis methodology. Check list on p 1897 can be used to assess this (or any other systematic review); For more advanced discussion see also Moher 1999.

Abstract: **PURPOSE:** Evidence-based medicine guidelines based on venographic end points recommend in-hospital prophylaxis with low-molecular-weight heparin (LMWH) in patients having elective hip surgery. Emerging data suggest that out-of-hospital use may offer additional protection; however, uncertainty remains about the risk-benefit ratio. To provide clinicians with a practical pathway for translating clinical research into practice, we systematically reviewed trials comparing extended out-of-hospital LMWH prophylaxis versus placebo. **DATA SOURCES:** Studies were identified by 1) searching PubMed, MEDLINE, and the Cochrane Library Database for reports published from January 1976 to May 2001; 2) reviewing references from retrieved articles; 3) scanning abstracts from conference proceedings; and 4) contacting pharmaceutical companies and investigators of the original reports. **STUDY SELECTION:** Randomized, controlled trials comparing extended out-of-hospital prophylaxis with LMWH versus placebo in patients having elective hip arthroplasty. **DATA EXTRACTION:** Two reviewers extracted data independently. Reviewers evaluated study quality by using a validated four-item instrument. **DATA SYNTHESIS:** Six of seven original articles met the defined inclusion criteria. The

included studies were double-blind trials that used proper randomization procedures. Compared with placebo, extended out-of-hospital prophylaxis decreased the frequency of all episodes of deep venous thrombosis (placebo rate, 150 of 666 patients [22.5%]; relative risk, 0.41 [95% CI, 0.32 to 0.54; $P < 0.001$]), proximal venous thrombosis (placebo rate, 76 of 678 patients [11.2%]; relative risk, 0.31 [CI, 0.20 to 0.47; $P < 0.001$]), and symptomatic venous thromboembolism (placebo rate, 36 of 862 patients [4.2%]; relative risk, 0.36 [CI, 0.20 to 0.67; $P = 0.001$]). Major bleeding was rare, occurring in only one patient in the placebo group. **CONCLUSIONS:** Extended LMWH prophylaxis showed consistent effectiveness and safety in the trials (regardless of study variations in clinical practice and length of hospital stay) for venographic deep venous thrombosis and symptomatic venous thromboembolism. The aggregate findings support the need for extended out-of-hospital prophylaxis in patients undergoing hip arthroplasty surgery.

Bradley, E. H., E. S. Holmboe, et al. (2001). "A qualitative study of increasing beta-blocker use after myocardial infarction: Why do some hospitals succeed?" *Jama* 285(20): 2604-2611.

Type of Question: Therapy **Beginner / Intermediate Qualitative / In-depth interviews.**

Teaching Notes: Excellent study for consideration of how qualitative research is done and what it can contribute to the medical literature that is distinct from quantitative research

Abstract: **CONTEXT:** Based on evidence that beta-blockers can reduce mortality in patients with acute myocardial infarction (AMI), many hospitals have initiated performance improvement efforts to increase prescription of beta-blockers at discharge. Determination of the factors associated with such improvements may provide guidance to hospitals that have been less successful in increasing beta-blocker use. **OBJECTIVES:** To identify factors that may influence the success of improvement efforts to increase beta-blocker use after AMI and to develop a taxonomy for classifying such efforts. **DESIGN, SETTING, AND PARTICIPANTS:** Qualitative study in which data were gathered from in-depth interviews conducted in March-June 2000 with 45 key physician, nursing, quality management, and administrative participants at 8 US hospitals chosen to represent a range of hospital sizes, geographic regions, and changes in beta-blocker use rates between October 1996 and September 1999. **MAIN OUTCOME MEASURES:** Initiatives, strategies, and approaches to improve care for patients with AMI. **RESULTS:** The interviews revealed 6 broad factors that characterized hospital-based improvement efforts: goals of the efforts, administrative support, support among clinicians, design and implementation of improvement initiatives, use of data, and modifying variables. Hospitals with greater improvements in beta-blocker use over time demonstrated 4 characteristics not found in hospitals with less or no improvement: shared goals for improvement, substantial administrative support, strong physician leadership advocating beta-blocker use, and use of credible data feedback. **CONCLUSIONS:** This study provides a context for understanding efforts to improve care in the hospital setting by describing a taxonomy for classifying and evaluating such efforts. In addition, the study suggests possible elements of successful efforts to increase beta-blocker use for patients with AMI.

Shelton, R. C., M. B. Keller, et al. (2001). "Effectiveness of St John's wort in major depression: a randomized controlled trial." *Jama* 285(15): 1978-1986.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Strong Methodology, very well described Interesting, topic (herbal preparations) that have broad impact due to OTC availability; Largely an equivalence trial, however there are some differences so you can calculate NNTs for those measures. Good discussion points: Nice Trial Flow design (fig 1) for discussion on methods; Can discuss intention to treat Has a great table of prior evidence with study limitations listed; GREAT for discussion of methodology issues. Prior reports have shown impact of St. John's Wort, so it is interesting to discuss why this paper might have different findings (i.e., different methods? Different populations of patients? Greater numbers of patients?)

Abstract: **CONTEXT:** Extracts of St John's wort are widely used to treat depression. Although more than 2 dozen clinical trials have been conducted with St John's wort, most have significant flaws in design and do not enable meaningful interpretation. **OBJECTIVE:** To compare the efficacy and safety of a standardized extract of St John's wort with placebo in outpatients with major depression. **DESIGN AND SETTING:** Randomized, double-blind, placebo-controlled clinical trial conducted between November 1998 and January 2000 in 11 academic medical centers in the United States. **PARTICIPANTS:** Two hundred

adult outpatients (mean age, 42.4 years; 67.0% female; 85.9% white) diagnosed as having major depression and having a baseline Hamilton Rating Scale for Depression (HAM-D) score of at least 20. INTERVENTION: Participants completed a 1-week, single-blind run-in of placebo, then were randomly assigned to receive either St John's wort extract (n = 98; 900 mg/d for 4 weeks, increased to 1200 mg/d in the absence of an adequate response thereafter) or placebo (n = 102) for 8 weeks. MAIN OUTCOME MEASURES: The primary outcome measure was rate of change on the HAM-D over the treatment period. Secondary measures included the Beck Depression Inventory (BDI), Hamilton Rating Scale for Anxiety (HAM-A), the Global Assessment of Function (GAF) scale, and the Clinical Global Impression-Severity and -Improvement scales (CGI-S and CGI-I). RESULTS: The random coefficient analyses for the HAM-D, HAM-A, CGI-S, and CGI-I all showed significant effects for time but not for treatment or time-by-treatment interaction (for HAM-D scores, $P < .001$, $P = .16$, and $P = .58$, respectively). Analysis of covariance showed nonsignificant effects for BDI and GAF scores. The proportion of participants achieving an a priori definition of response did not differ between groups. The number reaching remission of illness was significantly higher with St John's wort than with placebo ($P = .02$), but the rates were very low in the full intention-to-treat analysis (14/98 [14.3%] vs 5/102 [4.9%], respectively). St John's wort was safe and well tolerated. Headache was the only adverse event that occurred with greater frequency with St John's wort than placebo (39/95 [41%] vs 25/100 [25%], respectively). CONCLUSION: In this study, St John's wort was not effective for treatment of major depression.

Keller, M. B., J. P. McCullough, et al. (2000). "A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression." *N Engl J Med* 342(20): 1462-1470.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Excellent RCT methodology with three randomized arms in this controlled trial. Good discussion points: Good opportunity for discussion of intention to treat. Also clear reporting of results including all reasons for lost to follow up, makes the critical appraisal exercise straightforward. In terms of results, one trickier point is that the primary outcome is a score on the 24-item HRSD scale. Thus, in order to calculate proportion responding, you have to define what change in scale is going to count as a 'satisfactory' therapeutic response. Other good discussion regarding blinding, and attempts to minimize measurement error.

Abstract: BACKGROUND: Patients with chronic forms of major depression are difficult to treat, and the relative efficacy of medications and psychotherapy is uncertain. METHODS: We randomly assigned 681 adults with a chronic nonpsychotic major depressive disorder to 12 weeks of outpatient treatment with nefazodone (maximal dose, 600 mg per day), the cognitive behavioral-analysis system of psychotherapy (16 to 20 sessions), or both. At base line, all patients had scores of at least 20 on the 24-item Hamilton Rating Scale for Depression (indicating clinically significant depression). Remission was defined as a score of 8 or less at weeks 10 and 12. For patients who did not have remission, a satisfactory response was defined as a reduction in the score by at least 50 percent from base line and a score of 15 or less. Raters were unaware of the patients' treatment assignments. RESULTS: Of the 681 patients, 662 attended at least one treatment session and were included in the analysis of response. The overall rate of response (both remission and satisfactory response) was 48 percent in both the nefazodone group and in the psychotherapy group, as compared with 73 percent in the combined-treatment group. ($P < 0.001$ for both comparisons). Among the 519 subjects who completed the study, the rates of response were 55 percent in the nefazodone group and 52 percent in the psychotherapy group, as compared with 85 percent in the combined-treatment group ($P < 0.001$ for both comparisons). The rates of withdrawal were similar in the three groups. Adverse events in the nefazodone group were consistent with the known side effects of the drug (e.g., headache, somnolence, dry mouth, nausea, and dizziness). CONCLUSIONS: Although about half of patients with chronic forms of major depression have a response to short-term treatment with either nefazodone or a cognitive behavioral-analysis system of psychotherapy, the combination of the two is significantly more efficacious than either treatment alone.

Damoiseaux, R. A., F. A. van Balen, et al. (2000). "Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years." *Bmj* 320(7231): 350-354.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Fairly simple design with clear participant flow diagrams. The inclusion criteria and diagnostic criteria provide an opportunity to discuss how patient selection may bias the results in this study. Good discussion points: Applicable to parents and pediatricians alike. May provoke some interesting discussion about outcomes of interest and the conclusions that the authors draw from the data.

Abstract: **OBJECTIVE:** To determine the effect of antibiotic treatment for acute otitis media in children between 6 months and 2 years of age. **DESIGN:** Practice based, double blind, randomised, placebo controlled trial. **SETTING:** 53 general practices in the Netherlands. **SUBJECTS:** 240 children aged 6 months to 2 years with the diagnosis of acute otitis media. **INTERVENTION:** Amoxicillin 40 mg/kg/day in three doses. **MAIN OUTCOME MEASURES:** Persistent symptoms at day four and duration of fever and pain or crying, or both. Otoscopy at days four and 11, tympanometry at six weeks, and use of analgesic. **RESULTS:** Persistent symptoms at day four were less common in the amoxicillin group (risk difference 13%; 95% confidence interval 1% to 25%). The median duration of fever was two days in the amoxicillin group versus three in the placebo group ($P=0.004$). No significant difference was observed in duration of pain or crying, but analgesic consumption was higher in the placebo group during the first 10 days (4.1 v 2.3 doses, $P=0.004$). In addition, no otoscopic differences were observed at days four and 11, and tympanometric findings at six weeks were similar in both groups. **CONCLUSIONS:** Seven to eight children aged 6 to 24 months with acute otitis media needed to be treated with antibiotics to improve symptomatic outcome at day four in one child. This modest effect does not justify prescription of antibiotics at the first visit, provided close surveillance can be guaranteed.

Moher, D., D. J. Cook, et al. (1999). "Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses." Lancet **354**(9193): 1896-1900.

Type of Question: Therapy **Intermediate Meta analysis.**

Teaching Notes: Important question which prompts good discussion of risks v. benefits v. cost. Good Discussion Points: Strengths: Well designed with clear description of methods. Can use methods to prompt vocabulary discussion for concepts pertaining to Meta-analysis (e.g. methods for validity assessment, summary treatment effects, sensitivity analysis, heterogeneity); Weaknesses: Variety of interventions can become very confusing to learners. More Advanced Discussion: might consider getting the QUOROM statement that is referenced in the methods of the paper (p. 859) for more in depth discussion of Meta-analysis methodology. Check list on p 1897 can be used to assess this (or any other systematic review); See also Hull 2001.

Abstract: **BACKGROUND:** The Quality of Reporting of Meta-analyses (QUOROM) conference was convened to address standards for improving the quality of reporting of meta-analyses of clinical randomised controlled trials (RCTs). **METHODS:** The QUOROM group consisted of 30 clinical epidemiologists, clinicians, statisticians, editors, and researchers. In conference, the group was asked to identify items they thought should be included in a checklist of standards. Whenever possible, checklist items were guided by research evidence suggesting that failure to adhere to the item proposed could lead to biased results. A modified Delphi technique was used in assessing candidate items. **FINDINGS:** The conference resulted in the QUOROM statement, a checklist, and a flow diagram. The checklist describes our preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. It is organised into 21 headings and subheadings regarding searches, selection, validity assessment, data abstraction, study characteristics, and quantitative data synthesis, and in the results with "trial flow", study characteristics, and quantitative data synthesis; research documentation was identified for eight of the 18 items. The flow diagram provides information about both the numbers of RCTs identified, included, and excluded and the reasons for exclusion of trials. **INTERPRETATION:** We hope this report will generate further thought about ways to improve the quality of reports of meta-analyses of RCTs and that interested readers, reviewers, researchers, and editors will use the QUOROM statement and generate ideas for its improvement.

Bent, S., S. Saint, et al. (1999). "Antibiotics in acute bronchitis: a meta-analysis." Am J Med **107**(1): 62-67.

Type of Question: Therapy **Intermediate Systematic review / Meta analysis.**

Teaching Notes: There are nice tables and figures that are classic for systematic review and meta-analysis. Good discussion points: This is a good paper for discussion of 'effect size,' (what you do when the papers in your study don't measure the same outcomes..) However, this may slightly confuse those who are not fully comfortable with meta-analysis.

Abstract: **PURPOSE:** Most patients with acute bronchitis who seek medical care are treated with antibiotics, although the effectiveness of this intervention is uncertain. We performed a meta-analysis of randomized, controlled trials to estimate the effectiveness of antibiotics in the treatment of acute bronchitis. **SUBJECTS AND METHODS:** English-language studies published January 1966 to April 1998 were retrieved using MEDLINE, bibliographies, and consultation with experts. Only randomized trials that enrolled otherwise healthy patients with a diagnosis of acute bronchitis, used an antibiotic in the treatment group and a placebo in the control group, and provided sufficient data to calculate an effect size were included. **RESULTS:** We identified eight randomized controlled trials that satisfied all inclusion criteria. These studies used one of three antibiotics (erythromycin, doxycycline, trimethoprim/sulfamethoxazole). The use of antibiotics decreased the duration of cough and sputum production by approximately one-half day (summary effect size 0.21; 95% CI, 0.05 to 0.36). For specific symptoms, there were nonsignificant trends favoring the use of antibiotics: a decrease of 0.4 days of purulent sputum (95% CI, -0.1 to 0.8), a decrease of 0.5 days of cough (95% CI, -0.1 to 1.1), and a decrease of 0.3 days lost from work (95% CI, -0.6 to 1.1). **CONCLUSION:** This meta-analysis suggests a small benefit from the use of the antibiotics erythromycin, doxycycline, or trimethoprim/sulfamethoxazole in the treatment of acute bronchitis in otherwise healthy patients. As this small benefit must be weighed against the risk of side effects and the societal cost of increasing antibiotic resistance, we believe that the use of antibiotics is not justified in these patients.

Raina, P., D. Waltner-Toews, et al. (1999). "Influence of companion animals on the physical and psychological health of older people: an analysis of a one-year longitudinal study." J Am Geriatr Soc 47(3): 323-329.

Type of Question: Therapy **Beginner Cohort.**

Teaching Notes: Easy concept for any audience to grasp, regardless of background or comfort level in medicine, so you can focus on methodology. Good discussion points. What practical/logistical problems might make this a difficult question to answer with a RCT? Discuss cohort selection. Discuss alternative ways that a cohort of community-dwelling elderly could be selected and enrolled...and how different cohort selection strategies might yield different results. How does the fact that this is an observational rather than randomized study impact whether we trust the conclusions? How might confounders play a role in the results?

Abstract: **OBJECTIVE:** To examine whether companion animals or attachment to a companion animal was associated with changes in physical and psychological health in older people and whether the relationships between physical and psychological health and human social networks were modified by the presence or absence of a companion animal. **DESIGN:** A 1-year longitudinal study with standardized telephone interview data collected at baseline and repeated at 1-year **SETTING:** Wellington County, Ontario, Canada **PARTICIPANTS:** An age- and sex stratified random sample (baseline n = 1054; follow-up n = 995) of noninstitutionalized adults aged 65 and older (mean age = 73, SD +/- 6.3) **MEASUREMENTS:** Social Network Activity was measured using a family and non-family social support scale, participation in an organized social group, involvement in the affairs of the social group, the practice of confiding in others, feelings of loneliness, and the perceived presence of support in a crisis situation. Chronic conditions were measured as the current number of selected health problems. Pet ownership was assessed by the report of owning a dog or a cat and the Lexington Attachment to Pets Scale score. Physical health was assessed as the ability to perform Activities of Daily Living (ADLs). Psychological health was measured as a summed score comprising the level of satisfaction regarding one's health, family and friend relationships, job, finances, life in general, overall happiness, and perceived mental health. Sociodemographic variables assessed include subject age, sex, marital status, living arrangements, education, household income, and major life events. **RESULTS:** Pet owners were younger, currently married or living with someone, and more physically active than non-pet owners. The ADL level of respondents who did not currently own pets deteriorated more on average (beta = -.270, P = .040) than that of respondents who currently owned pets after adjusting for other variables during the 1-

year period. No statistically significant direct association was observed between pet ownership and change in psychological well-being ($P > .100$). However, pet ownership significantly modified the relationship between social support and the change in psychological well-being ($P = .001$) over a 1-year period. **CONCLUSIONS:** The results demonstrate the benefits of pet ownership in maintaining or slightly enhancing ADL levels of older people. However, a more complex relationship was observed between pet ownership and an older person's well-being.

Burgio, K. L., J. L. Locher, et al. (1998). "**Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial.**" *Jama* **280**(23): 1995-2000.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Good, well done RCT with clear methods including a patient flow diagram (fig. 2) which can be used for teaching; Some tricky thinking for the NNT calculations (hint: look at figure 3 to help you out...) Good discussion points: Can discuss 'stratification'; Can discuss intention to treat; Interesting spectrum of outcomes

Abstract: **CONTEXT:** Urinary incontinence is a common condition caused by many factors with several treatment options. **OBJECTIVE:** To compare the effectiveness of biofeedback-assisted behavioral treatment with drug treatment and a placebo control condition for the treatment of urge and mixed urinary incontinence in older community-dwelling women. **DESIGN:** Randomized placebo-controlled trial conducted from 1989 to 1995. **SETTING:** University-based outpatient geriatric medicine clinic. **PATIENTS:** A volunteer sample of 197 women aged 55 to 92 years with urge urinary incontinence or mixed incontinence with urge as the predominant pattern. Subjects had to have urodynamic evidence of bladder dysfunction, be ambulatory, and not have dementia. **INTERVENTION:** Subjects were randomized to 4 sessions (8 weeks) of biofeedback-assisted behavioral treatment, drug treatment (with oxybutynin chloride, possible range of doses, 2.5 mg daily to 5.0 mg 3 times daily), or a placebo control condition. **MAIN OUTCOME MEASURES:** Reduction in the frequency of incontinent episodes as determined by bladder diaries, and patients' perceptions of improvement and their comfort and satisfaction with treatment. **RESULTS:** For all 3 treatment groups, reduction of incontinence was most pronounced early in treatment and progressed more gradually thereafter. Behavioral treatment, which yielded a mean 80.7% reduction of incontinence episodes, was significantly more effective than drug treatment (mean 68.5% reduction; $P=.04$) and both were more effective than the placebo control condition (mean 39.4% reduction; $P<.001$ and $P=.009$, respectively). Patient-perceived improvement was greatest for behavioral treatment (74.1% "much better" vs 50.9% and 26.9% for drug treatment and placebo, respectively). Only 14.0% of patients receiving behavioral treatment wanted to change to another treatment vs 75.5% in each of the other groups. **CONCLUSION:** Behavioral treatment is a safe and effective conservative intervention that should be made more readily available to patients as a first-line treatment for urge and mixed incontinence.

Rowbotham, M., N. Harden, et al. (1998). "**Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial.**" *Jama* **280**(21): 1837-1842.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: This is a pivotal study of widely used agent for neuropathic pain. Good for discussing principles of pain research, a very important clinical issue ("the fifth vital sign"); Good Discussion Points: Excellent for discussion of pros and cons of scales as outcome measures; Good to understand strengths and weaknesses of mean scale scores versus percent responder rates between groups when reporting key trial outcomes (note: can't calculate NNT from scale scores) Can teach concept of minimally detectable differences, clinically meaningful differences; Can discuss difference between intention to treat and 'efficacy-evaluable' analyses (Data collection and statistical analysis page 1838)

Abstract: **CONTEXT:** Postherpetic neuralgia (PHN) is a syndrome of often intractable neuropathic pain following herpes zoster (shingles) that eludes effective treatment in many patients. **OBJECTIVE:** To determine the efficacy and safety of the anticonvulsant drug gabapentin in reducing PHN pain. **DESIGN:** Multicenter, randomized, double-blind, placebo-controlled, parallel design, 8-week trial conducted from August 1996 through July 1997. **SETTING:** Sixteen US outpatient clinical centers. **PARTICIPANTS:** A total of 229 subjects were randomized. **INTERVENTION:** A 4-week titration period to

a maximum dosage of 3600 mg/d of gabapentin or matching placebo. Treatment was maintained for another 4 weeks at the maximum tolerated dose. Concomitant tricyclic antidepressants and/or narcotics were continued if therapy was stabilized prior to study entry and remained constant throughout the study. **MAIN OUTCOME MEASURES:** The primary efficacy measure was change in the average daily pain score based on an 11-point Likert scale (0, no pain; 10, worst possible pain) from baseline week to the final week of therapy. Secondary measures included average daily sleep scores, Short-Form McGill Pain Questionnaire (SF-MPQ), Subject Global Impression of Change and investigator-rated Clinical Global Impression of Change, Short Form-36 (SF-36) Quality of Life Questionnaire, and Profile of Mood States (POMS). Safety measures included the frequency and severity of adverse events. **RESULTS:** One hundred thirteen patients received gabapentin, and 89 (78.8%) completed the study; 116 received placebo, and 95 (81.9%) completed the study. By intent-to-treat analysis, subjects receiving gabapentin had a statistically significant reduction in average daily pain score from 6.3 to 4.2 points compared with a change from 6.5 to 6.0 points in subjects randomized to receive placebo ($P < .001$). Secondary measures of pain as well as changes in pain and sleep interference showed improvement with gabapentin ($P < .001$). Many measures within the SF-36 and POMS also significantly favored gabapentin ($P < .05$ or $P = .01$). Somnolence, dizziness, ataxia, peripheral edema, and infection were all more frequent in the gabapentin group, but withdrawals were comparable in the 2 groups (15 [13.3%] in the gabapentin group vs 11 [9.5%] in the placebo group). **CONCLUSIONS:** Gabapentin is effective in the treatment of pain and sleep interference associated with PHN. Mood and quality of life also improve with gabapentin therapy.

de Ferranti, S. D., J. P. Ioannidis, et al. (1998). "Are amoxicillin and folate inhibitors as effective as other antibiotics for acute sinusitis? A meta-analysis." *Bmj* 317(7159): 632-637.

Type of Question: Therapy **Beginner / Intermediate Systematic review / Meta analysis.**

Teaching Notes: There are nice tables and figures that are classic for systematic review and meta-analysis. Good discussion points: Good discussion of both a positive finding (antibiotics vs. placebo) and also negative finding (cheap vs. expensive antibiotics). Also good to discuss cost implications.

Abstract: **OBJECTIVES:** To examine whether antibiotics are indicated in treating uncomplicated acute sinusitis and, if so, whether newer and more expensive antibiotics with broad spectra of antimicrobial activity are more effective than amoxicillin or folate inhibitors. **DESIGN:** Meta-analysis of randomised trials. **SETTING:** Outpatient clinics. **SUBJECTS:** 2717 patients with acute sinusitis or acute exacerbation of chronic sinusitis from 27 trials. **INTERVENTIONS:** Any antibiotic versus placebo; amoxicillin or folate inhibitors versus newer, more expensive antibiotics. **MAIN OUTCOME MEASUREMENTS:** Clinical failures and cures. **RESULTS:** Compared with placebo, antibiotics decreased the incidence of clinical failures by half (risk ratio 0.54 (95% confidence interval 0.37 to 0.79)). Risk of clinical failure among 1553 randomised patients was not meaningfully decreased with more expensive antibiotics as compared with amoxicillin (risk ratio 0.86 (0.62 to 1.19); risk difference 0.9 fewer failures per 100 patients (1.4 more failures to 3.1 fewer failures per 100 patients)). The results were similar for other antibiotics versus folate inhibitors (risk ratio 1.01 (0.52 to 1.97)), but data were sparse ($n=410$) and of low quality. **CONCLUSIONS:** Amoxicillin and folate inhibitors are essentially as effective as more expensive antibiotics for the initial treatment of uncomplicated acute sinusitis. Small differences in efficacy may exist, but are unlikely to be clinically important.

Johnson, D. W., S. Jacobson, et al. (1998). "A comparison of nebulized budesonide, intramuscular dexamethasone, and placebo for moderately severe croup." *N Engl J Med* 339(8): 498-503.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Fabulous methodology, clearly written; Easy NNT calculations. Note: this paper is of relevance to pediatricians, but also to anyone who has ever had a child with croup! Good discussion points: Awesome paper for discussion of blinding and the challenges that come up; Intention to treat analysis; For those who might want a greater challenge, you can discuss sample size calculations and type I error (page 500); Could address some issues of ethics including study termination

Abstract: **BACKGROUND:** In children with croup, treatment with nebulized budesonide decreases symptoms, but it is uncertain how budesonide compares with dexamethasone, the conventional therapy for croup, and whether either reduces the rate of hospitalization. **METHODS:** We

performed a double-blind, randomized trial involving 144 children with moderately severe croup. The children were treated with racpinephrine and a single dose of 4 mg of nebulized budesonide (48 children), 0.6 mg of intramuscular dexamethasone per kilogram of body weight (47 children), or placebo (49 children). The children were assessed before treatment and then hourly for five hours after treatment. Physicians who were unaware of the treatment assignments determined the children's need for further treatment and hospitalization. RESULTS: The characteristics of the groups were similar at base line, including the types of viruses identified, the types of croup, and the clinical severity of the illness. The overall rates of hospitalization were 71 percent in the placebo group (35 of 49 children), 38 percent in the budesonide group (18 of 48 children), and 23 percent in the dexamethasone group (11 of 47 children) (unadjusted $P=0.001$ for the comparison of budesonide with placebo, $P<0.001$ for the comparison of dexamethasone with placebo, and $P=0.18$ for the comparison of budesonide with dexamethasone). Children treated with budesonide or dexamethasone had a greater improvement in croup scores than those given placebo ($P=0.03$ and $P<0.001$, respectively), and those treated with dexamethasone had a greater improvement than those treated with budesonide ($P=0.003$). CONCLUSIONS: In children with moderately severe croup, treatment with intramuscular dexamethasone or nebulized budesonide resulted in more rapid clinical improvement than did the administration of placebo, with dexamethasone offering the greatest improvement. Treatment with either glucocorticoid resulted in fewer hospitalizations.

Stevens, B., A. Taddio, et al. (1997). "The efficacy of sucrose for relieving procedural pain in neonates--a systematic review and meta-analysis." *Acta Paediatr* 86(8): 837-842.

Type of Question: Therapy **Beginner / Intermediate Systematic review / Meta analysis.**

Teaching Notes: Straightforward methods that describe both the selection of articles as well as the assessment of quality of the methods. Good discussion points: Good paper for anyone who has ever had a child that underwent a procedure.

Abstract: The objective was to determine the efficacy and optimal dose of sucrose for relieving procedural pain in neonates. Data were obtained using MEDLINE, EMBASE, Reference Update and personal files and assessed for quality of the methods. Data from all randomized controlled trials where term and preterm neonates received a heelstick or venipuncture were examined for the efficacy of different sucrose doses (0.18 g, 0.24 g, 0.48 g or 0.50 g, 1.0 g) and water (placebo). The primary outcome was the proportion of time crying during 3 min after the painful stimulus. Data were combined across studies using a random effects model, adapted for use with single groups, producing a point estimate and 95% confidence interval (CI). Thirteen trials were identified; eight were rejected as data were inappropriate, non-extractable, or the primary outcome was not measured. Five studies provided data on 271 infants. The proportion of time crying did not differ between 0.18 g of sucrose and water ($p > 0.05$) but was significantly lower in all other sucrose groups. There were no differences in proportion of time crying between term and preterm neonates. Sucrose reduced the proportion of time crying during painful procedures in neonates. The 0.18 g dose of sucrose was ineffective. Doses of 0.24 g (2 ml of 12% sucrose solution) were most effective. A dose of 0.50 g provided no additional benefit.

Brandjes, D. P., H. R. Buller, et al. (1997). "Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis." *Lancet* 349(9054): 759-762.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Good, straightforward RCT methods; Easy NNT (number needed to treat) calculations. Good discussion points: Discussion of the strengths and weaknesses of subjective and objective outcomes; Can discuss the difference between time sensitive analysis (figure 2) as compared with proportions of patients who have responded at a particular time. Those wishing to take on a slightly greater challenge can discuss Kaplan-Meier Analysis (page 760 and figure 2)

Abstract: BACKGROUND: Post-thrombotic syndrome varies from mild oedema to incapacitating swelling with pain and ulceration. We investigated the rate of post-thrombotic syndrome after a first episode of deep-vein thrombosis and assessed the preventive effect of direct application of a sized-to-fit graded compression stocking. METHODS: Patients with a first episode of venogram-proven proximal deep-vein thrombosis were randomly assigned no stockings (the control group) or made-to-measure graded compression elastic stockings for at least 2 years. Post-thrombotic syndrome was assessed with a standard scoring system that combined clinical characteristics and objective leg measurements. Patients

were assessed every 3 months during the first 2 years, and every 6 months thereafter for at least 5 years. The cumulative incidence of mild-to-moderate post-thrombotic syndrome was the primary outcome measure. **FINDINGS:** Of the 315 consecutive outpatients considered for inclusion, 44 were excluded and 77 did not consent to take part. 194 patients were randomly assigned compression stockings (n = 96) or no stockings (n = 98). The median follow-up was 76 months (range 60-96) in both groups. Mild-to-moderate post-thrombotic syndrome (score ≥ 3 plus one clinical sign) occurred in 19 (20%) patients in the stocking group and in 46 (47%) control-group patients ($p < 0.001$). 11 (11%) patients in the stocking group developed severe post-thrombotic syndrome (score ≥ 4), compared with 23 (23%) patients in the control group ($p < 0.001$). In both groups, most cases of post-thrombotic syndrome occurred within 24 months of the acute thrombotic event. **INTERPRETATION:** About 60% of patients with a first episode of proximal deep-vein thrombosis develop post-thrombotic syndrome within 2 years. A sized-to-fit compression stocking reduced this rate by about 50%.

(1997). "The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group." *N Engl J Med* 336(8): 525-533.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: This is a sample teaching package; Solid Methodology; Landmark paper in internal medicine; Important and controversial clinical question (Dig: to treat or not to treat?); Good discussion points: Can discuss both equivalency (outcomes that did not show difference) and also positive findings (can calculate an NNT- number needed to treat); Can discuss the balance of benefits of therapy vs. potential harms; Good clinical applicability discussion can follow; Does a 'good' paper ever grow old? (i.e. does publication date matter?).. if so, when?

Abstract: **BACKGROUND:** The role of cardiac glycosides in treating patients with chronic heart failure and normal sinus rhythm remains controversial. We studied the effect of digoxin on mortality and hospitalization in a randomized, double-blind clinical trial. **METHODS:** In the main trial, patients with a left ventricular ejection fraction of 0.45 or less were randomly assigned to digoxin (3397 patients) or placebo (3403 patients) in addition to diuretics and angiotensin-converting-enzyme inhibitors (median dose of digoxin, 0.25 mg per day; average follow-up, 37 months). In an ancillary trial of patients with ejection fractions greater than 0.45, 492 patients were randomly assigned to digoxin and 496 to placebo. **RESULTS:** In the main trial, mortality was unaffected. There were 1181 deaths (34.8 percent) with digoxin and 1194 deaths (35.1 percent) with placebo (risk ratio when digoxin was compared with placebo, 0.99; 95 percent confidence interval, 0.91 to 1.07; $P=0.80$). In the digoxin group, there was a trend toward a decrease in the risk of death attributed to worsening heart failure (risk ratio, 0.88; 95 percent confidence interval, 0.77 to 1.01; $P=0.06$). There were 6 percent fewer hospitalizations overall in that group than in the placebo group, and fewer patients were hospitalized for worsening heart failure (26.8 percent vs. 34.7 percent; risk ratio, 0.72; 95 percent confidence interval, 0.66 to 0.79; $P<0.001$). In the ancillary trial, the findings regarding the primary combined outcome of death or hospitalization due to worsening heart failure were consistent with the results of the main trial. **CONCLUSIONS:** Digoxin did not reduce overall mortality, but it reduced the rate of hospitalization both overall and for worsening heart failure. These findings define more precisely the role of digoxin in the management of chronic heart failure.

Oler, A., M. A. Whooley, et al. (1996). "Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis." *Jama* 276(10): 811-815.

Type of Question: Therapy **Beginner / Intermediate Systematic Review / Meta Analysis.**

Teaching Notes: Important paper that directed clinical practice with respect to the use of aspirin and heparin. Good figures for discussing systematic review, confidence intervals, heterogeneity.

Abstract: **OBJECTIVE:** To estimate the risk of myocardial infarction (MI) and death in patients with unstable angina who are treated with aspirin plus heparin compared with patients treated with aspirin alone. **DATA SOURCES:** Studies were retrieved using MEDLINE, bibliographies, and consultation with experts. **STUDY SELECTION:** Only published trials that enrolled patients with unstable angina, randomized participants to aspirin plus heparin vs aspirin alone, and reported incidence of myocardial infarction or death were included in the meta-analysis. **DATA EXTRACTION:** Patient outcomes including MI or death, recurrent ischemic pain, and major bleeding during randomized treatment; revascularization

procedures after randomization; and MI or death during the 2 to 12 weeks following randomization were extracted by 2 authors, 1 of whom was blinded to the journal, institution, and author of each study. DATA SYNTHESIS: Six randomized trials were included. The overall summary relative risk (RR) of MI or death during randomized treatment was 0.67 (95% confidence interval [CI], 0.44-1.02) in patients with unstable angina treated with aspirin plus heparin compared with those treated with aspirin alone. The summary RRs for secondary endpoints in patients treated with aspirin plus heparin compared with those treated with aspirin alone were 0.68 (95% CI, 0.40-1.17) for recurrent ischemic pain; 0.82 (95% CI, 0.56-1.20) for MI or death 2 to 12 weeks following randomization; 1.03 (95% CI, 0.74-1.43) for revascularization; and 1.99 (95% CI, 0.52-7.65) for major bleeding. We found no statistically significant heterogeneity among individual study findings. CONCLUSIONS: Our findings are consistent with a 33% reduction in risk of MI or death in patients with unstable angina treated with aspirin plus heparin compared with those treated with aspirin alone. The bulk of evidence suggests that most patients with unstable angina should be treated with both heparin and aspirin.

Duffy, L. M., J. Cleary, et al. (1995). "**Clean intermittent catheterization: safe, cost-effective bladder management for male residents of VA nursing homes.**" *J Am Geriatr Soc* 43(8): 865-870.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Straightforward RCT with clear methods; Equivalence trial, therefore can not calculate an NNT. Good discussion points: Great multidisciplinary paper; Can discuss 'stratification' (this is hidden in the methods sections, you may need to figure out where it shows up...) Might use this paper to discuss sample size see page 868); Good discussion of costs

Abstract: OBJECTIVES: To compare the safety and cost of clean versus sterile intermittent bladder catheterization in male nursing home residents. To provide evidence to support the hypothesis that intermittent catheterization is a valid, alternative method of bladder management in male residents of long-term care in whom urinary retention is a documented problem. DESIGN: Randomized clinical trial. SETTING: Three long-term care sites having predominantly male populations. PARTICIPANTS: Eighty male veterans, residents of three long-term care facilities, ranging in age from 36 to 96 years with a mean age of 72. INTERVENTIONS: Standardized procedures for clean and sterile intermittent catheterization (IC) were implemented by staff nurses at each site. Patients were randomized into clean and sterile IC groups. Nursing time and catheterization equipment usage were recorded using bar code readers. Clinical data were collected from the medical chart. Treatment of urinary tract infection was prescribed by the medical personnel responsible for each individual resident. MEASUREMENTS: We compared the number of treatment episodes for symptomatic bacteriuria between groups randomized to receive either clean or sterile intermittent catheterization. Laboratory analysis of blood and urine was done on predetermined days. Control variables were research site and patient history of urinary tract infection within the last 6 months. A cost comparison of nursing time and equipment usage for the two catheterization techniques was also performed. RESULTS: No significant differences were found between clean and sterile groups with regard to number of treatment episodes, time to first infection, type of organism cultured, or cost of antibiotic treatment. The cost of sterile technique was considerably higher both in terms of nursing time and supplies. CONCLUSIONS: Findings from this study demonstrate that clean technique intermittent catheterization is a safe and cost-effective bladder management technique with male, nursing home residents, despite the frailty of this high risk population. An annual savings of approximately \$1460 per patient in nursing time and catheterization supplies could be anticipated if a patient were catheterized an average of four times per day substituting clean IC technique for sterile IC technique.

Tyring, S., R. A. Barbarash, et al. (1995). "**Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group.**" *Ann Intern Med* 123(2): 89-96.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Solid Methodology; Difficult to calculate NNT (number needed to treat)--but it can be done....Good discussion points: End points that are 'time' events; "intention to treat" vs. "efficacy-evaluable" analysis; Does it matter who paid for the trial? (See grant support page 95)

Abstract: OBJECTIVE: To document the effects of treatment with famciclovir on the acute signs and symptoms of herpes zoster and postherpetic neuralgia. DESIGN: A randomized, double-blind, placebo-controlled, multicenter trial. SETTING: 36 centers in the United States, Canada, and Australia. PATIENTS: 419 immunocompetent adults with uncomplicated herpes zoster. INTERVENTION: Patients were assigned within 72 hours of rash onset to famciclovir, 500 mg; famciclovir, 750 mg; or placebo, three times daily for 7 days. MEASUREMENTS: Lesions were assessed daily for as long as 14 days until full crusting occurred and then weekly until the lesions healed. Viral cultures were obtained daily while vesicles were present. Pain was assessed at each of the visits at which lesions were examined and then monthly for 5 months after the lesions healed. Safety was assessed throughout the study. RESULTS: Famciclovir was well tolerated, with a safety profile similar to that of placebo. Famciclovir accelerated lesion healing and reduced the duration of viral shedding. Most importantly, famciclovir recipients had faster resolution of postherpetic neuralgia (approximately twofold faster) than placebo recipients; differences between the placebo group and both the 500-mg famciclovir group (hazard ratio, 1.7 [95% CI, 1.1 to 2.7]) and the 750-mg famciclovir group (hazard ratio, 1.9 [CI, 1.2 to 2.9]) were statistically significant ($P = 0.02$ and 0.01 , respectively). The median duration of postherpetic neuralgia was reduced by approximately 2 months. CONCLUSIONS: Oral famciclovir, 500 mg or 750 mg three times daily for 7 days, is an effective and well-tolerated therapy for herpes zoster that decreases the duration of the disease's most debilitating complication, postherpetic neuralgia.

Pagliaro, L., G. D'Amico, et al. (1992). "Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment." *Ann Intern Med* 117(1): 59-70.

Type of Question: Therapy **Intermediate / Advanced Systematic review / Meta analysis.**

Teaching Notes: Very good article for discussion of heterogeneity. (There is significant heterogeneity here...There are many good figures for illustration. However, the many figures and different kind of graphical representations may intimidate those who are not familiar with how to look at a systematic review. This is good for those who wish to take on a more challenging paper, but should be avoided by more novice meta-analysis learners.

Abstract: OBJECTIVE: To assess the effectiveness of beta-blockers and endoscopic sclerotherapy in the prevention of first bleeding and reduction of mortality in patients with cirrhosis and esophagogastric varices. DATA SOURCES: Pertinent studies were selected using MEDLINE (1980 to 1990), reference lists from published articles or reviews, and congress abstract lists. STUDY SELECTION: Randomized trials comparing beta-blockers or sclerotherapy with a nonactive treatment. Nine randomized clinical trials of beta-blockers and 19 trials of sclerotherapy were reviewed. Seven trials of beta-blockers and 15 of sclerotherapy were published as full papers. DATA EXTRACTION: Crude rates of bleeding and death in treated and control groups were extracted from each trial by three independent observers according to the intention-to-treat principle. The quality of published papers was systematically assessed and scored. DATA SYNTHESIS: The Mantel-Haenszel-Peto method was used for statistical evaluation of heterogeneity and for pooling of the results. No substantial heterogeneity was found, and the incidence of bleeding in trials of beta-blockers was significantly reduced (pooled odds ratio, 0.54; 95% CI, 0.39 to 0.74), particularly in patients with large or medium-sized varices or in those with varices and a hepatic vein pressure gradient above 12 mm Hg; however, only a trend toward reduced mortality was obtained. Sclerotherapy trials were highly heterogeneous in the direction of the treatment effects on both bleeding (pooled odds ratio, 0.6; CI, 0.49 to 0.74) and mortality (pooled odds ratio, 0.76; CI, 0.61 to 0.94). The quality of the trials and the rate of bleeding in the untreated groups were the major sources of heterogeneity. The favorable results of sclerotherapy were obtained in trials with high bleeding rates among controls; several of these trials had a low quality score. CONCLUSIONS: Beta-blockers may be recommended for prevention of first bleeding in cirrhotic patients with varices who have a high risk for bleeding. The effectiveness of sclerotherapy remains undetermined. Further trials in high-risk patients may prove useful if improved criteria to predict bleeding risk become available.

Winblad, B., K. Engedal, et al. (2001). "A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD." *Neurology* 57(3): 489-495.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Strong RCT methodology Good discussion points: Paper is good for calculations of risk ratio, absolute risk reduction and number needed to treat.

Abstract: **OBJECTIVE:** To evaluate the long-term clinical efficacy and safety of donepezil versus placebo over 1 year in patients with mild to moderate AD. **METHODS:** Patients (n = 286; mean age, 72.5 years) with possible or probable AD from five Northern European countries were randomized to receive either donepezil (n = 142; 5 mg/day for 28 days, followed by 10 mg/day) or placebo (n = 144) for 1 year. **RESULTS:** The study was completed by 66.9% of the donepezil- and 67.4% of the placebo-treated patients. The benefit of donepezil over placebo was demonstrated by the Gottfries-Brane-Steen (a global assessment for rating dementia symptoms) total score at weeks 24, 36, and 52 ($p < 0.05$) and at the study end point (week 52, last observation carried forward; $p = 0.054$). Advantages of donepezil over placebo were also observed in cognition and activities of daily living (ADL) assessed by the Mini-Mental State Examination at weeks 24, 36, and 52, and the end point ($p < 0.02$) and by the Progressive Deterioration Scale at week 52 and the end point ($p < 0.05$). Adverse events (AE) were recorded for 81.7% of donepezil- and 75.7% of placebo-treated patients, with 7% of donepezil- and 6.3% of placebo-treated patients discontinuing because of AE. Treatment response to donepezil was not predicted by APOE genotype or sex in this population. **CONCLUSION:** As the first 1-year, multinational, double-blinded, placebo-controlled study of a cholinesterase inhibitor in AD, these data support donepezil as a well tolerated and effective long-term treatment for patients with AD, with benefits over placebo on global assessment, cognition, and ADL.

Bajwa, E. K., N. T. Ayas, et al. (2005). "Interferon-gamma1b therapy in idiopathic pulmonary fibrosis: a metaanalysis." *Chest* 128(1): 203-206.

Type of Question: Therapy **Intermediate Meta-analysis.**

Teaching Notes: This can be taught as a package. First exercise goes through the user's guide for therapy and the first article. The second exercise goes through the user's guide for meta-analysis. It helps illustrate some of the points of the validity of the systematic review because the learner's have had a sneak peak at the underlying data. Teach with: Part 1: Raghu G et al. A Placebo-controlled trial of interferon gamma 1b in patients with idiopathic pulmonary fibrosis

Abstract: **CONTEXT:** Despite the investigation of multiple therapeutic options, idiopathic pulmonary fibrosis (IPF) remains a devastating, progressively fatal disease. Much interest has focused on the use of interferon (IFN)-gamma1b therapy, but the efficacy of this treatment has not been proven. **OBJECTIVE:** To determine whether IFN treatment reduces mortality in patients with IPF. **DESIGN:** A meta-analysis of randomized controlled trials evaluating the use of IFN-gamma1b as treatment for IPF. **MAIN OUTCOME MEASURE:** Mortality in patients treated with IFN-gamma1b was compared to mortality in patients treated with control therapies. **RESULTS:** A total of three studies involving 390 patients was included in the analysis. IFN-gamma1b therapy was associated with reduced mortality (hazard ratio [HR], 0.418; 95% confidence interval [CI], 0.253 to 0.690; $p = 0.0003$). A comparison of mortality at different time points revealed that IFN-gamma1b therapy was associated with significantly reduced mortality at 1 year (0.0861; 95% CI, 0.0244 to 0.1478; $p = 0.0063$), 18 months (0.1682; 95% CI, 0.1065 to 0.2299; $p < 0.0001$), 650 days (0.1939; 95% CI, 0.1386 to 0.2492; $p < 0.0001$), and 2 years (0.2652; 95% CI, 0.1652 to 0.3652; $p < 0.0001$). **CONCLUSION:** When the results of multiple studies are combined in a meta-analysis, IFN-gamma1b therapy is associated with reduced mortality.

Eidelman, R. S., D. Hollar, et al. (2004). "Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease." *Arch Intern Med* 164(14): 1552-1556.

Type of Question: Therapy **Intermediate Systematic Review.**

Teaching Notes: Very poor quality systematic review. Give very little information on methods. Good Discussion Points: This is an excellent article to use in combination with the Shekelle article to highlight the differences in quality. This is a good example of inappropriate pooling of studies. Pooling combined antioxidants with vitamin E alone. Good example of how poor quality articles can be published in well regarded journals. Can be used to force learners to think about how they would have done the review.

Abstract: **BACKGROUND:** Observational epidemiological studies consistently show that individuals who choose to take high amounts of vitamin E through diet or supplements experience

cardiovascular benefits, for which basic research provides plausible mechanisms. However, because the size of the postulated benefit is small to moderate, the confounding inherent in observational studies is as great as the effect size. Before the availability of randomized evidence, about 1 in 4 adults was taking vitamin E supplements in the United States. **METHODS:** We conducted a computerized search of the English-language literature from 1990 to the present and found 7 large-scale randomized trials of the effectiveness vitamin E in the treatment and prevention of cardiovascular disease. Data were available on myocardial infarction, stroke, or cardiovascular death. **RESULTS:** Six of the 7 trials showed no significant effect of vitamin E on cardiovascular disease. In an overview, vitamin E had neither a statistically significant nor a clinically important effect on any important cardiovascular event (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.94-1.03) or its components: nonfatal myocardial infarction (OR, 1.00; 95% CI, 0.92-1.09), nonfatal stroke (OR, 1.03; 95% CI, 0.93-1.14), or cardiovascular death (OR, 1.00; 95% CI, 0.94-1.05). **CONCLUSIONS:** The ORs and CIs provide strong support for a lack of statistically significant or clinically important effects of vitamin E on cardiovascular disease. The use of agents of proven lack of benefit, especially those easily available over the counter, may contribute to underuse of agents of proven benefit and failure to adopt healthy lifestyles.

Shekelle, P. G., S. C. Morton, et al. (2004). "Effect of supplemental vitamin E for the prevention and treatment of cardiovascular disease." *J Gen Intern Med* 19(4): 380-389.

Type of Question: Therapy **Beginner Systematic Review.**

Teaching Notes: High quality systematic review. Easy to understand therapy and outcomes if teaching a group from mixed specialties. It is a treatment that many people are still on contrary to the evidence. A little bit complicated since it looked at vitamin E alone and vitamin E in combination as 2 separate analyses in the same paper. Good Discussion Points: Validity of SR since it is extremely well done with extensive search and description of methodology. Discussion of heterogeneity. Main outcome did not show heterogeneity, but the secondary outcomes did. This can be seen statistically as well as in the Forest plots. They also mention the I2 statistic as well as χ^2 , so can use this for advanced learners. Given the differences between studies it is a good example of when to pool and when not to. I focus on the main outcome of mortality to try and simplify this long article. ACP Journal Club reviews this article. See also Miller, E. *Annals of Internal Med* Jan 4 2005 and Eidelman RS. *Annals of Internal Med* 2004.

Abstract: **OBJECTIVE:** To evaluate and synthesize the evidence on the effect of supplements of vitamin E on the prevention and treatment of cardiovascular disease. **DESIGN:** Systematic review of placebo-controlled randomized controlled trials; meta-analysis where justified. **MEASUREMENTS AND MAIN RESULTS:** Eighty-four eligible trials were identified. For the outcomes of all-cause mortality, cardiovascular mortality, fatal or nonfatal myocardial infarction, and blood lipids, neither supplements of vitamin E alone nor vitamin E given with other agents yielded a statistically significant beneficial or adverse pooled relative risk (for example, pooled relative risk of vitamin E alone = 0.96 [95% confidence interval (CI), 0.84 to 1.10]; 0.97 [95% CI, 0.80 to 1.90]; and 0.72 [95% CI, 0.51 to 1.02] for all-cause mortality, cardiovascular mortality, and nonfatal myocardial infarction, respectively). **CONCLUSIONS:** There is good evidence that vitamin E supplementation does not beneficially or adversely affect cardiovascular outcomes.

Raghu, G., K. K. Brown, et al. (2004). "A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis." *N Engl J Med* 350(2): 125-133.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: This can be taught as a package. First exercise goes through the user's guide for therapy and the first article. The second exercise goes through the user's guide for meta-analysis. It helps illustrate some of the points of the validity of the systematic review because the learner's have had a sneak peak at the underlying data. Teach with: Part 2: Bajwa EK et al Interferon gamma 1 b therapy in idiopathic pulmonary fibrosis. A meta-analysis *NEJM* 2004: 350: 125-133.

Abstract: **BACKGROUND:** Idiopathic pulmonary fibrosis is a progressive, fatal disease with no known efficacious therapy. **METHODS:** In a double-blind, multinational trial, we randomly assigned 330 patients with idiopathic pulmonary fibrosis that was unresponsive to corticosteroid therapy to receive subcutaneous interferon gamma-1b or placebo. **RESULTS:** Over a median of 58 weeks, interferon gamma-1b therapy did not significantly affect the primary end point of progression-free survival, defined

as the time to disease progression or death, and no significant treatment effect was observed on measures of lung function, gas exchange, or the quality of life. Ten percent of patients in the interferon gamma-1b group died, as compared with 17 percent of patients in the placebo group ($P=0.08$). Treatment with interferon gamma-1b was associated with more frequent constitutional symptoms. However, the rates of treatment adherence and premature discontinuation of treatment were similar in the two groups. More pneumonias were reported among patients in the interferon gamma-1b group, but the incidence of severe or life-threatening respiratory tract infections was similar in the two groups. **CONCLUSIONS:** In a well-defined population of patients with idiopathic pulmonary fibrosis, interferon gamma-1b did not affect progression-free survival, pulmonary function, or the quality of life. Owing to the size and duration of the trial, a clinically significant survival benefit could not be ruled out.

Konstantinides, S., A. Geibel, et al. (2002). "**Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism.**" *N Engl J Med* 347(15): 1143-1150.

Type of Question: Therapy **Intermediate / Advanced RCT.**

Teaching Notes: Prestigious journal and high impact study that has widely been interpreted to justify administration of thrombolytic therapy to relatively stable patients with pulmonary embolism and evidence of right heart strain or failure. It is the only RCT addressing this question. Good discussion points: This is ultimately a negative example. Basic methodology is sound. However there are major problems with the composite outcome, unblinding of the study with respect to one component of the composite and it was also a 'trial stopped early'. A great exercise in unraveling spin in industry sponsored high profile trials.

Abstract: **BACKGROUND:** The use of thrombolytic agents in the treatment of hemodynamically stable patients with acute submassive pulmonary embolism remains controversial. **METHODS:** We conducted a study of patients with acute pulmonary embolism and pulmonary hypertension or right ventricular dysfunction but without arterial hypotension or shock. The patients were randomly assigned in double-blind fashion to receive heparin plus 100 mg of alteplase or heparin plus placebo over a period of two hours. The primary end point was in-hospital death or clinical deterioration requiring an escalation of treatment, which was defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter. **RESULTS:** Of 256 patients enrolled, 118 were randomly assigned to receive heparin plus alteplase and 138 to receive heparin plus placebo. The incidence of the primary end point was significantly higher in the heparin-plus-placebo group than in the heparin-plus-alteplase group ($P=0.006$), and the probability of 30-day event-free survival (according to Kaplan-Meier analysis) was higher in the heparin-plus-alteplase group ($P=0.005$). This difference was due to the higher incidence of treatment escalation in the heparin-plus-placebo group (24.6 percent vs. 10.2 percent, $P=0.004$), since mortality was low in both groups (3.4 percent in the heparin-plus-alteplase group and 2.2 percent in the heparin-plus-placebo group, $P=0.71$). Treatment with heparin plus placebo was associated with almost three times the risk of death or treatment escalation that was associated with heparin plus alteplase ($P=0.006$). No fatal bleeding or cerebral bleeding occurred in patients receiving heparin plus alteplase. **CONCLUSIONS:** When given in conjunction with heparin, alteplase can improve the clinical course of stable patients who have acute submassive pulmonary embolism and can prevent clinical deterioration requiring the escalation of treatment during the hospital stay.

Humphrey, L. L., B. K. Chan, et al. (2002). "**Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease.**" *Ann Intern Med* 137(4): 273-284.

Type of Question: Therapy **Intermediate Meta-analysis.**

Teaching Notes: Pros: Can discuss Cochrane controlled trials register. Validity criteria for inclusion of studies into the SR. Search strategies for SRs. Cons: Long, Dated

Abstract: **PURPOSE:** To evaluate the value of hormone replacement therapy (HRT) in the primary prevention of cardiovascular disease (CVD) and coronary artery disease (CAD). **DATA SOURCES:** MEDLINE and Cochrane databases were searched for all primary prevention studies reporting CVD or CAD incidence, mortality, or both in association with HRT; reference lists, letters, editorials, and reviews were also reviewed. **DATA EXTRACTION:** All studies were reviewed, abstracted, and rated for quality. **STUDY SELECTION:** Only studies of good or fair quality, according to U.S.

Preventive Services Task Force (USPSTF) criteria, were included in the detailed review and meta-analysis. DATA SYNTHESIS: The summary relative risk with any HRT use was 0.75 (95% credible interval [CrI], 0.42 to 1.23) for CVD mortality and 0.74 (CrI, 0.36 to 1.45) for CAD mortality. The summary relative risk with any use was 1.28 (CrI, 0.86 to 2.00) for CVD incidence and 0.87 (CrI, 0.62 to 1.21) for CAD incidence. Further analysis of studies adjusting for socioeconomic status, as well as other major CAD risk factors, showed a summary relative risk of 1.07 (CrI, 0.79 to 1.48) for CAD incidence associated with any HRT use. Similar results were found when the analysis was stratified by studies adjusting for alcohol consumption, exercise, or both, in addition to other major risk factors, suggesting confounding by these factors. CONCLUSIONS: This meta-analysis differs from previous meta-analyses by evaluating potential explanatory variables of the relationship between HRT, CVD, and CAD. The adjusted meta-analysis is consistent with recent randomized trials that have shown no benefit in the secondary or primary prevention of CVD events. A valid answer to the role of HRT in the primary prevention of CVD will best come from randomized, controlled trials.

Dorian, P., D. Cass, et al. (2002). "Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation." *N Engl J Med* 346(12): 884-890.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Easy to do in a 1 hour session. Valid with important findings Teaching points: Challenges of doing RCT in real life = good for discussions about efficacy vs effectiveness. Allows for good discussion on NNT. Allows for good discussion on intention to treat

Abstract: BACKGROUND: Lidocaine has been the initial antiarrhythmic drug treatment recommended for patients with ventricular fibrillation that is resistant to conversion by defibrillator shocks. We performed a randomized trial comparing intravenous lidocaine with intravenous amiodarone as an adjunct to defibrillation in victims of out-of-hospital cardiac arrest. METHODS: Patients were enrolled if they had out-of-hospital ventricular fibrillation resistant to three shocks, intravenous epinephrine, and a further shock; or if they had recurrent ventricular fibrillation after initially successful defibrillation. They were randomly assigned in a double-blind manner to receive intravenous amiodarone plus lidocaine placebo or intravenous lidocaine plus amiodarone placebo. The primary end point was the proportion of patients who survived to be admitted to the hospital. RESULTS: In total, 347 patients (mean [±SD] age, 67±14 years) were enrolled. The mean interval between the time at which paramedics were dispatched to the scene of the cardiac arrest and the time of their arrival was 7±3 minutes, and the mean interval from dispatch to drug administration was 25±8 minutes. After treatment with amiodarone, 22.8 percent of 180 patients survived to hospital admission, as compared with 12.0 percent of 167 patients treated with lidocaine (P=0.009; odds ratio, 2.17; 95 percent confidence interval, 1.21 to 3.83). Among patients for whom the time from dispatch to the administration of the drug was equal to or less than the median time (24 minutes), 27.7 percent of those given amiodarone and 15.3 percent of those given lidocaine survived to hospital admission (P=0.05). CONCLUSIONS: As compared with lidocaine, amiodarone leads to substantially higher rates of survival to hospital admission in patients with shock-resistant out-of-hospital ventricular fibrillation.

McMahon, S. R., M. E. Rimsza, et al. (1997). "Parents can dose liquid medication accurately." *Pediatrics* 100(3 Pt 1): 330-333.

Type of Question: Therapy **Beginner / Intermediate RCT.**

Teaching Notes: Good RCT about an intervention other than a drug. Reasonably good methodology. Largely ignored paper that could have important implications. Discussion points: Role of complete follow-up. Role of concealment of randomization and allocation can be discussed. Easy calculations of NNT. Can change management strategy for pediatricians!

Abstract: OBJECTIVE: To determine whether parental errors in dosing liquid medication can be decreased through education. DESIGN: Randomized convenience sample stratified to three study groups. SETTING: General pediatric clinic, largely indigent and Latino. PATIENTS: A total of 45 English-speaking and 45 Spanish-speaking children diagnosed with otitis media and treated with an antibiotic suspension. INTERVENTION: Group 1 patients received the prescription and verbal instructions. Group 2 patients received the prescription and a syringe, then the correct dose was demonstrated. Group 3 patients received the prescription, a syringe with a line marked at the correct dose, and a demonstration.

After returning from the pharmacy, parents administered the medication under observation. Parents in group 1 used a dispensing device similar to that planned for home use. The other groups used the syringe. After observation but before discharge, everyone received a syringe with a line marked at the correct dose. Patients were seen again at approximately 1 month, and parents demonstrated how much medication they had administered. **MAIN OUTCOME MEASURE:** Percent of parents who administered the correct dose. **RESULTS:** Patients in group 1 received between 32% and 147% of the correct dose, with only 11 of 30 (37%) receiving the correct dose (± 0.2 mL). In group 2, 25 of 30 (83%) parents administered the correct dose, and in group 3, 30 of 30 (100%) gave the correct dose. Simultaneous logistic regression indicated that accuracy of dosage differed across instructional groups and language. At follow-up, 23 of 26 parents demonstrated the correct dose. **CONCLUSION:** Education can decrease medication dosing errors made by both Spanish-speaking and English-speaking parents. Effectiveness was also shown at follow-up.

Martinez, F. J., S. Safran, et al. (2005). "The clinical course of patients with idiopathic pulmonary fibrosis." *Ann Intern Med* **142**(12 Pt 1): 963-967.

Type of Question: Therapy **Beginner/Intermediate RCT.**

Teaching Notes: Solid Methodology; Landmark paper in internal medicine; Important and controversial clinical question (Dig: to treat or not to treat?); Good discussion points: Can discuss both equivalency (outcomes that did not show difference) and also positive findings (can calculate an NNT- number needed to treat); Can discuss the balance of benefits of therapy vs. potential harms; Good clinical applicability discussion can follow; Does a 'good' paper ever grow old? (i.e. does publication date matter?).. if so, when?

Abstract: **BACKGROUND:** Prospective data defining the clinical course in idiopathic pulmonary fibrosis (IPF) are sparse. **OBJECTIVE:** To analyze the clinical course of patients with mild to moderate IPF. **DESIGN:** Analysis of data from the placebo group of a randomized, controlled trial evaluating interferon-gamma1b. **SETTING:** Academic and community medical centers. **PATIENTS:** 168 patients in the placebo group of a trial evaluating interferon-gamma1b. **MEASUREMENTS:** Measures of physiology and dyspnea assessed at 12-week intervals; hospitalizations; and the pace of deterioration and cause of death over a median period of 76 weeks. **RESULTS:** Physiologic variables changed minimally during the study. However, 23% of patients required hospitalization for a respiratory disorder and 21% died. Idiopathic pulmonary fibrosis was the primary cause of death in 89% of patients who died, and an apparent acute clinical deterioration preceded death in 47% of these patients. **LIMITATIONS:** The instrument used to define the pace of deterioration and cause of death was applied retrospectively. **CONCLUSIONS:** Recognition of the common occurrence of acute fatal deterioration in patients with mild to moderate IPF has important implications for monitoring patients and supports early referral for lung transplantation.

Hochman, J. S., G. A. Lamas, et al. (2006). "Coronary intervention for persistent occlusion after myocardial infarction." *N Engl J Med* **355**(23): 2395-2407.

Type of Question: Therapy **RCT.**

Teaching Notes: Great teaching points

Abstract: **BACKGROUND:** It is unclear whether stable, high-risk patients with persistent total occlusion of the infarct-related coronary artery identified after the currently accepted period for myocardial salvage has passed should undergo percutaneous coronary intervention (PCI) in addition to receiving optimal medical therapy to reduce the risk of subsequent events. **METHODS:** We conducted a randomized study involving 2166 stable patients who had total occlusion of the infarct-related artery 3 to 28 days after myocardial infarction and who met a high-risk criterion (an ejection fraction of $<50\%$ or proximal occlusion). Of these patients, 1082 were assigned to routine PCI and stenting with optimal medical therapy, and 1084 were assigned to optimal medical therapy alone. The primary end point was a composite of death, myocardial reinfarction, or New York Heart Association (NYHA) class IV heart failure. **RESULTS:** The 4-year cumulative primary event rate was 17.2% in the PCI group and 15.6% in the medical therapy group (hazard ratio for death, reinfarction, or heart failure in the PCI group as compared with the medical therapy group, 1.16; 95% confidence interval [CI], 0.92 to 1.45; $P=0.20$). Rates of myocardial reinfarction (fatal and nonfatal) were 7.0% and 5.3% in the two groups, respectively (hazard

ratio, 1.36; 95% CI, 0.92 to 2.00; P=0.13). Rates of nonfatal reinfarction were 6.9% and 5.0%, respectively (hazard ratio, 1.44; 95% CI, 0.96 to 2.16; P=0.08); only six reinfarctions (0.6%) were related to assigned PCI procedures. Rates of NYHA class IV heart failure (4.4% vs. 4.5%) and death (9.1% vs. 9.4%) were similar. There was no interaction between treatment effect and any subgroup variable (age, sex, race or ethnic group, infarct-related artery, ejection fraction, diabetes, Killip class, and the time from myocardial infarction to randomization). **CONCLUSIONS:** 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 in stable patients with occlusion of the infarct-related artery 3 to 28 days after myocardial infarction. (ClinicalTrials.gov number, NCT00004562 [ClinicalTrials.gov].).

Dentali, F., J. D. Douketis, et al. (2007). "**Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients.**" *Ann Intern Med* 146(4): 278-288.

Type of Question: Therapy **Intermediate Meta-analysis.**

Teaching Notes: Paper of importance to internists, hospitalists, house officers and anyone who takes care of patients in the hospital. Clear methodology with excellent forest plots for teaching. Can use to illustrate a paper where results do not display any heterogeneity.

Abstract: **BACKGROUND:** Underutilization of anticoagulant prophylaxis may be due to lack of evidence that prophylaxis prevents clinically important outcomes in hospitalized medical patients at risk for venous thromboembolism. **PURPOSE:** To assess the effects of anticoagulant prophylaxis in reducing clinically important outcomes in hospitalized medical patients. **DATA SOURCES:** MEDLINE, EMBASE, and Cochrane databases were searched to September 2006 without language restrictions. **STUDY SELECTION:** Randomized trials comparing anticoagulant prophylaxis with no treatment in hospitalized medical patients. **DATA EXTRACTION:** Any symptomatic pulmonary embolism (PE), fatal PE, symptomatic deep venous thrombosis, all-cause mortality, and major bleeding. Pooled relative risks and associated 95% CIs were calculated. For treatment effects that were statistically significant, the authors determined the absolute risk reduction and the number needed to treat for benefit (NNT(B)) to prevent an outcome. **DATA SYNTHESIS:** 9 studies (n = 19 958) were included. During anticoagulant prophylaxis, patients had significant reductions in any PE (relative risk, 0.43 [CI, 0.26 to 0.71]; absolute risk reduction, 0.29%; NNT(B), 345) and fatal PE (relative risk, 0.38 [CI, 0.21 to 0.69]; absolute risk reduction, 0.25%; NNT(B), 400), a nonsignificant reduction in symptomatic deep venous thrombosis (relative risk, 0.47 [CI, 0.22 to 1.00]), and a nonsignificant increase in major bleeding (relative risk, 1.32 [CI, 0.73 to 2.37]). Anticoagulant prophylaxis had no effect on all-cause mortality (relative risk, 0.97 [CI, 0.79 to 1.19]). **LIMITATIONS:** 2 of 9 included studies were not double-blind. **CONCLUSIONS:** Anticoagulant prophylaxis is effective in preventing symptomatic venous thromboembolism during anticoagulant prophylaxis in at-risk hospitalized medical patients. Additional research is needed to determine the risk for venous thromboembolism in these patients after prophylaxis has been stopped.

Spiro, D. M., K. Y. Tay, et al. (2006). "**Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial.**" *Jama* 296(10): 1235-1241.

Type of Question: Therapy **Beginner/intermediate RCT.**

Teaching Notes: Relevant topic for pediatricians or acute care / ER providers (or anyone who has ever had a child with otitis media!) Clear simple methods with impressive results and easy math (NNT = approximately 2 for not filling antibiotic prescriptions). Paper also has very descriptive methods that allow discussion of the randomization process as well as blinding. Clear reporting as well as flow chart as well as description of intention to treat and "worst case sensitivity analysis"

Abstract: **CONTEXT:** Acute otitis media (AOM) is the most common diagnosis for which antibiotics are prescribed for children. Previous trials that have evaluated a "wait-and-see prescription" (WASP) for antibiotics, with which parents are asked not to fill the prescription unless the child either is not better or is worse in 48 hours, have excluded children with severe AOM. None of these trials were conducted in an emergency department. **OBJECTIVES:** To determine whether treatment of AOM using a WASP significantly reduces use of antibiotics compared with a "standard prescription" (SP) and to evaluate the effects of this intervention on clinical symptoms and adverse outcomes related to antibiotic use. **DESIGN, SETTING, AND PATIENTS:** A randomized controlled trial conducted between July 12,

2004, and July 11, 2005. Children with AOM aged 6 months to 12 years seen in an emergency department were randomly assigned to receive either a WASP or an SP. All patients received ibuprofen and otic analgesic drops for use at home. A research assistant, blinded to group assignment, conducted structured phone interviews 4 to 6, 11 to 14, and 30 to 40 days after enrollment to determine outcomes. MAIN OUTCOME MEASURES: Filling of the antibiotic prescription and clinical course. RESULTS: Overall, 283 patients were randomized either to the WASP group (n = 138) or the SP group (n = 145). Substantially more parents in the WASP group did not fill the antibiotic prescription (62% vs 13%; $P < .001$). There was no statistically significant difference between the groups in the frequency of subsequent fever, otalgia, or unscheduled visits for medical care. Within the WASP group, both fever (relative risk [RR], 2.95; 95% confidence interval [CI], 1.75 - 4.99; $P < .001$) and otalgia (RR, 1.62; 95% CI, 1.26 - 2.03; $P < .001$) were associated with filling the prescription. CONCLUSION: The WASP approach substantially reduced unnecessary use of antibiotics in children with AOM seen in an emergency department and may be an alternative to routine use of antimicrobials for treatment of such children. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00250900.

Philip, P., J. Taillard, et al. (2006). "The effects of coffee and napping on nighttime highway driving: a randomized trial." *Ann Intern Med* 144(11): 785-791.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: This is a randomized, partly blinded cross-over trial in which all drivers performed 4 sessions to allow comparisons. The study looked at effect of coffee and napping strategy on driving behaviors in those who are fatigued or driving at night. Very small sample (12 healthy young men), however for early learners or for illustrating principles of RCT, this trial can be material for great teaching. The topic is relevant to all audiences, especially educators given the 80 hour duty limit. Good paper for teaching results as the comparisons are simple and you can easily calculate NNT for preventing line crossings.

Abstract: BACKGROUND: Sleep-related accidents often involve healthy young persons who are driving at night. Coffee and napping restore alertness, but no study has compared their effects on real nighttime driving performances. OBJECTIVE: To test the effects of 125 mL of coffee (half a cup) containing 200 mg of caffeine, placebo (decaffeinated coffee containing 15 mg of caffeine), or a 30-minute nap (at 1:00 a.m.) in a car on nighttime driving performance. DESIGN: Double-blind, randomized, crossover study. SETTING: Sleep laboratory and open highway. PARTICIPANTS: 12 young men (mean age, 21.3 years [SD, 1.8]). MEASUREMENTS: Self-rated fatigue and sleepiness, inappropriate line crossings from video recordings during highway driving, and polysomnographic recordings during the nap and subsequent sleep. INTERVENTION: Participants drove 200 km (125 miles) between 6:00 p.m. and 7:30 p.m. (daytime reference condition) or between 2:00 a.m. and 3:30 a.m. (coffee, decaffeinated coffee, or nap condition). After intervention, participants returned to the laboratory to sleep. RESULTS: Nighttime driving performance was similar to daytime performance (0 to 1 line crossing) for 75% of participants after coffee (0 or 1 line crossing), for 66% after the nap ($P = 0.66$ vs. coffee), and for only 13% after placebo ($P = 0.041$ vs. nap; $P = 0.014$ vs. coffee). The incidence rate ratios for having a line crossing after placebo were 3.7 (95% CI, 1.2 to 11.0; $P = 0.001$) compared with coffee and 2.9 (CI, 1.7 to 5.1; $P = 0.021$) compared with nap. A statistically significant interindividual variability was observed in response to sleep deprivation and countermeasures. Sleep latencies and efficiency during sleep after nighttime driving were similar in the 3 conditions. LIMITATIONS: Only 1 dose of coffee and 1 nap duration were tested. Effects may differ in other patient or age groups. CONCLUSIONS: Drinking coffee or napping at night statistically significantly reduces driving impairment without altering subsequent sleep.

McFalls, E. O., H. B. Ward, et al. (2004). "Coronary-artery revascularization before elective major vascular surgery." *N Engl J Med* 351(27): 2795-2804.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: RCT of patients at risk for perioperative cardiac complications assigned to revascularization or no revascularization prior to elective major vascular surgery. landmark trial that changed thinking about perioperative cardiac risk assessment and intervention. Good paper for discussion of methods and incorporation of evidence into practice. Because the results are 'no difference' between groups, you can not calculate an NNT.

Abstract: BACKGROUND: The benefit of coronary-artery revascularization before elective major vascular surgery is unclear. METHODS: We randomly assigned patients at increased risk for perioperative cardiac complications and clinically significant coronary artery disease to undergo either revascularization or no revascularization before elective major vascular surgery. The primary end point was long-term mortality. RESULTS: Of 5859 patients scheduled for vascular operations at 18 Veterans Affairs medical centers, 510 (9 percent) were eligible for the study and were randomly assigned to either coronary-artery revascularization before surgery or no revascularization before surgery. The indications for a vascular operation were an expanding abdominal aortic aneurysm (33 percent) or arterial occlusive disease of the legs (67 percent). Among the patients assigned to preoperative coronary-artery revascularization, percutaneous coronary intervention was performed in 59 percent, and bypass surgery was performed in 41 percent. The median time from randomization to vascular surgery was 54 days in the revascularization group and 18 days in the group not undergoing revascularization ($P<0.001$). At 2.7 years after randomization, mortality in the revascularization group was 22 percent and in the no-revascularization group 23 percent (relative risk, 0.98; 95 percent confidence interval, 0.70 to 1.37; $P=0.92$). Within 30 days after the vascular operation, a postoperative myocardial infarction, defined by elevated troponin levels, occurred in 12 percent of the revascularization group and 14 percent of the no-revascularization group ($P=0.37$). CONCLUSIONS: Coronary-artery revascularization before elective vascular surgery does not significantly alter the long-term outcome. On the basis of these data, a strategy of coronary-artery revascularization before elective vascular surgery among patients with stable cardiac symptoms cannot be recommended.

Hebert, P. C., G. Wells, et al. (1999). "A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group." *N Engl J Med* 340(6): 409-417.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: An RCT of restrictive RBC transfusion strategy vs. liberal RBC transfusion strategy. Clear methods well reported. Good paper to discuss the concept of an equivalency trial. While you cannot calculate an NNT for the main results (as they show no difference), you can calculate an NNT for in hospital mortality which was different between groups.

Good paper to combine with Rao et al JAMA 2004; 292:155-1562

Abstract: BACKGROUND: To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients, we compared the rates of death from all causes at 30 days and the severity of organ dysfunction. METHODS: We enrolled 838 critically ill patients with euolemia after initial treatment who had hemoglobin concentrations of less than 9.0 g per deciliter within 72 hours after admission to the intensive care unit and randomly assigned 418 patients to a restrictive strategy of transfusion, in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g per deciliter and hemoglobin concentrations were maintained at 7.0 to 9.0 g per deciliter, and 420 patients to a liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 10.0 g per deciliter and hemoglobin concentrations were maintained at 10.0 to 12.0 g per deciliter. RESULTS: Overall, 30-day mortality was similar in the two groups (18.7 percent vs. 23.3 percent, $P=0.11$). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill -- those with an Acute Physiology and Chronic Health Evaluation II score of $< \text{or} = 20$ (8.7 percent in the restrictive-strategy group and 16.1 percent in the liberal-strategy group; $P=0.03$) -- and among patients who were less than 55 years of age (5.7 percent and 13.0 percent, respectively; $P=0.02$), but not among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; $P=0.69$). The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.3 percent vs. 28.1 percent, $P=0.05$). CONCLUSIONS: A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.

Hollingsworth, J. M., M. A. Rogers, et al. (2006). "Medical therapy to facilitate urinary stone passage: a meta-analysis." *Lancet* 368(9542): 1171-1179.

Type of Question: Therapy **Beginner Meta-analysis.**

Teaching Notes: The study pools relatively few studies of low methodological quality. Suitable for group exercises in which learners abstract data assess methodological quality of individual RCTS and then pool data.

Abstract: BACKGROUND: Medical therapies to ease urinary-stone passage have been reported, but are not generally used. If effective, such therapies would increase the options for treatment of urinary stones. To assess efficacy, we sought to identify and summarise all randomised controlled trials in which calcium-channel blockers or alpha blockers were used to treat urinary stone disease. METHODS: We searched MEDLINE, Pre-MEDLINE, CINAHL, and EMBASE, as well as scientific meeting abstracts, up to July, 2005. All randomised controlled trials in which calcium-channel blockers or alpha blockers were used to treat ureteral stones were eligible for inclusion in our analysis. Data from nine trials (number of patients=693) were pooled. The main outcome was the proportion of patients who passed stones. We calculated the summary estimate of effect associated with medical therapy use using random-effects and fixed-effects models. FINDINGS: Patients given calcium-channel blockers or alpha blockers had a 65% (absolute risk reduction=0.31 95% CI 0.25-0.38) greater likelihood of stone passage than those not given such treatment (pooled risk ratio 1.65; 95% CI 1.45-1.88). The pooled risk ratio for alpha blockers was 1.54 (1.29-1.85) and for calcium-channel blockers with steroids was 1.90 (1.51-2.40). The proportion of heterogeneity not explained by chance alone was 28%. The number needed to treat was 4. INTERPRETATION: Although a high-quality randomised trial is necessary to confirm its efficacy, our findings suggest that medical therapy is an option for facilitation of urinary-stone passage for patients amenable to conservative management, potentially obviating the need for surgery.

Jack, B. W., V. K. Chetty, et al. (2009). "**A reengineered hospital discharge program to decrease rehospitalization: a randomized trial.**" *Ann Intern Med* 150(3): 178-187.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Great for teaching principles of RCT methodology. Specifically good for teaching 1) randomization : sequence generation (blocked randomization scheme) and allocation concealment (opaque envelopes as well as varied block sizes); 2) blinding (who can be blinded when the intervention is a process enhancement)

Abstract: BACKGROUND: Emergency department visits and rehospitalization are common after hospital discharge. OBJECTIVE: To test the effects of an intervention designed to minimize hospital utilization after discharge. DESIGN: Randomized trial using block randomization of 6 and 8. Randomly arranged index cards were placed in opaque envelopes labeled consecutively with study numbers, and participants were assigned a study group by revealing the index card. SETTING: General medical service at an urban, academic, safety-net hospital. PATIENTS: 749 English-speaking hospitalized adults (mean age, 49.9 years). INTERVENTION: A nurse discharge advocate worked with patients during their hospital stay to arrange follow-up appointments, confirm medication reconciliation, and conduct patient education with an individualized instruction booklet that was sent to their primary care provider. A clinical pharmacist called patients 2 to 4 days after discharge to reinforce the discharge plan and review medications. Participants and providers were not blinded to treatment assignment. MEASUREMENTS: Primary outcomes were emergency department visits and hospitalizations within 30 days of discharge. Secondary outcomes were self-reported preparedness for discharge and frequency of primary care providers' follow-up within 30 days of discharge. Research staff doing follow-up were blinded to study group assignment. RESULTS: Participants in the intervention group (n = 370) had a lower rate of hospital utilization than those receiving usual care (n = 368) (0.314 vs. 0.451 visit per person per month; incidence rate ratio, 0.695 [95% CI, 0.515 to 0.937]; P = 0.009). The intervention was most effective among participants with hospital utilization in the 6 months before index admission (P = 0.014). Adverse events were not assessed; these data were collected but are still being analyzed. LIMITATION: This was a single-center study in which not all potentially eligible patients could be enrolled, and outcome assessment sometimes relied on participant report. CONCLUSION: A package of discharge services reduced hospital utilization within 30 days of discharge. FUNDING: Agency for Healthcare Research and Quality and National Heart, Lung, and Blood Institute, National Institutes of Health.

Walters, J. A., P. G. Gibson, et al. (2009). "**Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease.**" *Cochrane Database Syst Rev*(1): CD001288.

Type of Question: Therapy **Intermediate Metaanalysis.**

Teaching Notes: Good article for review of the critical appraisal of a systematic review as methods are clearly reported. Teaching point can be made when discussing the outcome of 'treatment failure'. Page 8 describes the different meanings for this composite outcome in the various studies. The question to focus on: are the various outcomes in the composite measure similar in importance to the patient? (all cause mortality, readmission, intensification of pharmacologic treatment). Forest plots are clear and do have plots with both significant heterogeneity (figure 2 $I^2 = 43\%$) and others with $I^2 = 0$.

Abstract: **BACKGROUND:** COPD is a common condition, mainly related to smoking. Acute exacerbations of COPD, usually related to superimposed infection, occur commonly and systemic corticosteroids are widely used in their management in combination with other treatments including antibiotics, oxygen supplementation and bronchodilators. **OBJECTIVES:** To determine the efficacy of corticosteroids, administered either parenterally or orally, on the outcomes of acute exacerbations of COPD. **SEARCH STRATEGY:** Searches were carried out using the Cochrane Airways Group COPD RCT register with additional studies sought in the bibliographies of randomised controlled trials and review articles. Authors of identified randomised controlled trials were contacted for other published and unpublished studies. The last search was carried out in August 2008. **SELECTION CRITERIA:** Randomised controlled trials comparing corticosteroids, administered either parenterally or orally, with appropriate placebo control. Other interventions e.g. bronchodilators and antibiotics were standardised. Clinical studies of acute asthma were excluded. **DATA COLLECTION AND ANALYSIS:** Data were extracted independently by two reviewers. Data measured but not reported were sought from authors of included studies. Trials were combined using Review Manager for analyses. **MAIN RESULTS:** Eleven studies ($n=1081$) fulfilled the inclusion criteria and 10 studies contributed data for analyses ($n=1051$). There were significantly fewer treatment failures within thirty days in patients given corticosteroid treatment, Odds Ratio (OR) 0.50; 95% confidence interval (CI) 0.36 to 0.69 and Hazard Ratio 0.78; 95% CI 0.63 to 0.97. It would have been necessary to treat 10 patients (95%CI 7 to 16) with corticosteroids to avoid one treatment failure in this time period. Duration of hospitalisation was significantly shorter with corticosteroid treatment, mean difference -1.22 days; 95% CI -2.26 to -0.18. For FEV1 there were significant treatment benefits with mean differences at the early time point (to 72 hours), 140 ml; 95% CI 90 to 190 ml and at end of treatment (up to 15 days) 80 ml; 95% confidence interval 10 to 160. There was a significant improvement in breathlessness and blood gases at both time points. There was no significant effect on mortality but an increased likelihood of an adverse event associated with corticosteroid treatment, OR 2.33; 95% CI 1.60 to 3.40. Overall one extra adverse effect occurred for every 5 people treated (95% CI 4 to 9). The risk of hyperglycaemia was significantly increased, OR 4.95; 95% CI 2.47 to 9.91. **AUTHORS' CONCLUSIONS:** Treatment of an exacerbation of COPD with oral or parenteral corticosteroids significantly reduces treatment failure and the need for additional medical treatment and shortens hospital stay. It increases the rate of improvement in lung function and dyspnoea and the improvement continues during treatment, but there is a significantly increase in the risk of an adverse drug event occurring. The optimal dose and length of treatment regime needs to be better defined.

Treanor, J. J., F. G. Hayden, et al. (2000). "Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group." *JAMA* 283(8): 1016-1024.

Type of Question: Therapy **Beginner**

Teaching Notes: Fairly straightforward RCT; good for teaching basic principles of validity criteria. Topic good for discussion about whether a 2000 year old article still has relevance, given the world-wide epidemic of H1N1 influenza.

Abstract: **CONTEXT:** Previous studies have shown oseltamivir, a neuraminidase inhibitor, to be effective in preventing influenza and treating experimental influenza. **OBJECTIVE:** To evaluate the efficacy and safety of oseltamivir in the treatment of naturally acquired influenza infection. **DESIGN:** Randomized, placebo-controlled, double-blind study conducted January through March 1998. **SETTING:** Sixty primary care and university health centers throughout the United States. **PARTICIPANTS:** A total of 629 healthy nonimmunized adults aged 18 to 65 years with febrile respiratory illness of no more than 36 hours' duration with temperature of 38 degrees C or more plus at least 1 respiratory symptom and 1 constitutional symptom. **INTERVENTIONS:** Individuals were randomized to 1 of 3 treatment groups with identical appearing pills: oral oseltamivir phosphate, 75 mg twice daily ($n = 211$) or 150 mg ($n = 209$) twice

daily, or placebo (n = 209). **MAIN OUTCOME MEASURES:** Duration and severity of illness in individuals infected with influenza. **RESULTS:** Two individuals withdrew before receiving medication and were excluded from further analyses. A total of 374 individuals (59.6%) were infected with influenza. Their duration of illness was reduced by more than 30% with both oseltamivir, 75 mg twice daily (median, 71.5 hours; $P < .001$), and oseltamivir, 150 mg twice daily (median, 69.9 hours; $P = .006$), compared with placebo (median, 103.3 hours). Severity of illness was reduced by 38% (median score, 597 score-hours; $P < .001$) with oseltamivir, 75 mg twice daily, and by 35% (median score, 626 score-hours; $P < .001$) with oseltamivir, 150 mg twice daily, vs placebo (median score, 963 score-hours). Oseltamivir treatment reduced the duration of fever and oseltamivir recipients returned to usual activities 2 to 3 days earlier than placebo recipients ($P < \text{or} = .05$). Secondary complications such as bronchitis and sinusitis occurred in 15% of placebo recipients compared with 7% of combined oseltamivir recipients ($P = .03$). Among all 629 subjects, oseltamivir reduced illness duration (76.3 hours and 74.3 hours for 75 mg and 150 mg, respectively, vs 97.0 hours for placebo; $P = .004$ for both comparisons) and illness severity (686 score-hours and 629 score-hours for 75 mg and 150 mg, respectively, vs 887 score-hours for placebo; $P < .001$ for both comparisons). Nausea and vomiting occurred more frequently in both oseltamivir groups (combined, 18.0% and 14.1%, respectively; $P = .002$) than in the placebo group (7.4% and 3.4%; $P < .001$). **CONCLUSIONS:** Our data suggest that oral oseltamivir treatment reduces the duration and severity of acute influenza in healthy adults and may decrease the incidence of secondary complications.

Drummond, M. B., E. C. Dasenbrook, et al. (2008). "Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis." *JAMA* 300(20): 2407-2416.

Type of Question: Therapy **Intermediate to Advanced Meta-analysis.**

Teaching Notes: Clearly reported meta-analysis on a somewhat controversial topic (inhaled steroids for COPD) with a controversial result (no change in mortality but increased pneumonia in treated group). This is also a good paper for discussing heterogeneity: mortality outcome in figure 2 ($I^2=0$), but pneumonia risk has significant heterogeneity indicating that it might not be okay to combine ($I^2=72\%$). This paper should be reserved for more advanced learners who are ready to grapple with more difficult issues. There is an ACP Journal Club summary of this paper, but remarkably they don't mention the heterogeneity issues.

Abstract: **CONTEXT:** Recent studies of inhaled corticosteroid (ICS) therapy for managing stable chronic obstructive pulmonary disease (COPD) have yielded conflicting results regarding survival and risk of adverse events. **OBJECTIVE:** To systematically review and quantitatively synthesize the effects of ICS therapy on mortality and adverse events in patients with stable COPD. **DATA SOURCES:** Search of MEDLINE, CENTRAL, EMBASE, CINAHL, Web of Science, and PsychInfo through February 9, 2008. **STUDY SELECTION:** Eligible studies were double-blind, randomized controlled trials comparing ICS therapy for 6 or more months with nonsteroid inhaled therapy in patients with COPD. **DATA EXTRACTION:** Two authors independently abstracted data including study characteristics, all-cause mortality, pneumonia, and bone fractures. The I^2 statistic was used to assess heterogeneity. Study-level data were pooled using a random-effects model (when $I^2 > \text{or} = 50\%$) or a fixed-effects model (when $I^2 < 50\%$). For the primary outcome of all-cause mortality at 1 year, our meta-analysis was powered to detect a 1.0% absolute difference in mortality, assuming a 2-sided alpha of .05 and power of 0.80. **RESULTS:** Eleven eligible randomized controlled trials (14,426 participants) were included. In trials with mortality data, no difference was observed in 1-year all-cause mortality (128 deaths among 4636 patients in the treatment group and 148 deaths among 4597 patients in the control group; relative risk [RR], 0.86; 95% confidence interval [CI], 0.68-1.09; $P = .20$; $I^2 = 0\%$). In the trials with data on pneumonia, ICS therapy was associated with a significantly higher incidence of pneumonia (777 cases among 5405 patients in the treatment group and 561 cases among 5371 patients in the control group; RR, 1.34; 95% CI, 1.03-1.75; $P = .03$; $I^2 = 72\%$). Subgroup analyses indicated an increased risk of pneumonia in the following subgroups: highest ICS dose (RR, 1.46; 95% CI, 1.10-1.92; $P = .008$; $I^2 = 78\%$), shorter duration of ICS use (RR, 2.12; 95% CI, 1.47-3.05; $P < .001$; $I^2 = 0\%$), lowest baseline forced expiratory volume in the first second of expiration (RR, 1.90; 95% CI, 1.26-2.85; $P = .002$; $I^2 = 0\%$), and combined ICS and bronchodilator therapy (RR, 1.57; 95% CI, 1.35-1.82; $P < .001$; $I^2 = 24\%$). **CONCLUSIONS:** Among patients with COPD, ICS therapy does not affect 1-year all-cause mortality. ICS therapy is

associated with a higher risk of pneumonia. Future studies should determine whether specific subsets of patients with COPD benefit from ICS therapy.

Duckworth, W., C. Abraira, et al. (2009). "**Glucose control and vascular complications in veterans with type 2 diabetes.**" *N Engl J Med* 360(2): 129-139.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: Clearly reported methods that allow discussion of RCT validity criteria. This is one of several papers to come out within a 6 month period that does not support more aggressive glucose management. Good for teaching Kaplan Meier curves as well as calculating Number needed to harm (NNH). (see also the ACCORD study NEJM 2008; 358:2545-59.)

Abstract: BACKGROUND: The effects of intensive glucose control on cardiovascular events in patients with long-standing type 2 diabetes mellitus remain uncertain. METHODS: We randomly assigned 1791 military veterans (mean age, 60.4 years) who had a suboptimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. Other cardiovascular risk factors were treated uniformly. The mean number of years since the diagnosis of diabetes was 11.5, and 40% of the patients had already had a cardiovascular event. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level, as compared with the standard-therapy group. The primary outcome was the time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. RESULTS: The median follow-up was 5.6 years. Median glycated hemoglobin levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. The primary outcome occurred in 264 patients in the standard-therapy group and 235 patients in the intensive-therapy group (hazard ratio in the intensive-therapy group, 0.88; 95% confidence interval [CI], 0.74 to 1.05; $P=0.14$). There was no significant difference between the two groups in any component of the primary outcome or in the rate of death from any cause (hazard ratio, 1.07; 95% CI, 0.81 to 1.42; $P=0.62$). No differences between the two groups were observed for microvascular complications. The rates of adverse events, predominantly hypoglycemia, were 17.6% in the standard-therapy group and 24.1% in the intensive-therapy group. CONCLUSIONS: Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications with the exception of progression of albuminuria ($P = 0.01$) [added]. (ClinicalTrials.gov number, NCT00032487.)

Gerstein, H. C., M. E. Miller, et al. (2008). "**Effects of intensive glucose lowering in type 2 diabetes (ACCORD Study).**" *N Engl J Med* 358(24): 2545-2559.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: Clearly reported methods that allow discussion of RCT validity criteria. This is one of several papers to come out within a 6 month period that does not support more aggressive glucose management. This study was stopped early for concerns about harm in the intensive insulin therapy group. You can discuss subgroup analysis (figure 3) (see also Duckworth et al. NEJM 2009; 360:129-39.)

Abstract: BACKGROUND: Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors. METHODS: In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up. RESULTS: At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as

compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001). **CONCLUSIONS:** As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

Wright, J. M. and V. M. Musini (2009). "**First-line drugs for hypertension.**" Cochrane Database Syst Rev(3): CD001841.

Type of Question: Therapy **Intermediate to Advanced Meta-analysis.**

Teaching Notes: This is an extensive review of first line therapy for hypertension including studies comparing major drug classes with placebo/ no treatment looking at outcomes of mortality, stroke and coronary artery disease. Although this meta-analysis is very long (60 pages), a teaching session could focus on particular parts, such as specific forest plots. There is also an ACP journal club summary that could serve as a central point of discussion. The key messages here are that there are the gaps between what we know (thiazides and ACE inhibitors decrease mortality) and what we do (a minority of patients with hypertension are on these drugs as first line therapies).

Abstract: **BACKGROUND:** Sustained elevated blood pressure, unresponsive to lifestyle measures, leads to a critically important clinical question: What class of drug to use first-line? This review answers that question. **OBJECTIVES:** Primary objective: To quantify the benefits and harms of the major first-line anti-hypertensive drug classes: thiazides, beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, alpha-blockers, and angiotensin II receptor blockers (ARB). **SEARCH STRATEGY:** Electronic search of MEDLINE (Jan. 1966-June 2008), EMBASE, CINAHL, the Cochrane clinical trial register, using standard search strategy of the hypertension review group with additional terms. **SELECTION CRITERIA:** Randomized trials of at least one year duration comparing one of 6 major drug classes with a placebo or no treatment. More than 70% of people must have BP >140/90 mmHg at baseline. **DATA COLLECTION AND ANALYSIS:** The outcomes assessed were mortality, stroke, coronary heart disease (CHD), cardiovascular events (CVS), decrease in systolic and diastolic blood pressure, and withdrawals due to adverse drug effects. Risk ratio (RR) and a fixed effects model were used to combine outcomes across trials. **MAIN RESULTS:** Of 57 trials identified, 24 trials with 28 arms, including 58,040 patients met the inclusion criteria. Thiazides (19 RCTs) reduced mortality (RR 0.89, 95% CI 0.83, 0.96), stroke (RR 0.63, 95% CI 0.57, 0.71), CHD (RR 0.84, 95% CI 0.75, 0.95) and CVS (RR 0.70, 95% CI 0.66, 0.76). Low-dose thiazides (8 RCTs) reduced CHD (RR 0.72, 95% CI 0.61, 0.84), but high-dose thiazides (11 RCTs) did not (RR 1.01, 95% CI 0.85, 1.20). Beta-blockers (5 RCTs) reduced stroke (RR 0.83, 95% CI 0.72, 0.97) and CVS (RR 0.89, 95% CI 0.81, 0.98) but not CHD (RR 0.90, 95% CI 0.78, 1.03) or mortality (RR 0.96, 95% CI 0.86, 1.07). ACE inhibitors (3 RCTs) reduced mortality (RR 0.83, 95% CI 0.72-0.95), stroke (RR 0.65, 95% CI 0.52-0.82), CHD (RR 0.81, 95% CI 0.70-0.94) and CVS (RR 0.76, 95% CI 0.67-0.85). Calcium-channel blocker (1 RCT) reduced stroke (RR 0.58, 95% CI 0.41, 0.84) and CVS (RR 0.71, 95% CI 0.57, 0.87) but not CHD (RR 0.77 95% CI 0.55, 1.09) or mortality (RR 0.86 95% CI 0.68, 1.09). No RCTs were found for ARBs or alpha-blockers. **AUTHORS' CONCLUSIONS:** First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

Hochman, J. S., G. A. Lamas, et al. (2006). "**Coronary intervention for persistent occlusion after myocardial infarction.**" N Engl J Med **355**(23): 2395-2407.

Type of Question: Therapy **RCT.**

Teaching Notes: Great teaching points

Abstract: **BACKGROUND:** It is unclear whether stable, high-risk patients with persistent total occlusion of the infarct-related coronary artery identified after the currently accepted period for myocardial salvage has passed should undergo percutaneous coronary intervention (PCI) in addition to receiving

optimal medical therapy to reduce the risk of subsequent events. **METHODS:** We conducted a randomized study involving 2166 stable patients who had total occlusion of the infarct-related artery 3 to 28 days after myocardial infarction and who met a high-risk criterion (an ejection fraction of <50% or proximal occlusion). Of these patients, 1082 were assigned to routine PCI and stenting with optimal medical therapy, and 1084 were assigned to optimal medical therapy alone. The primary end point was a composite of death, myocardial reinfarction, or New York Heart Association (NYHA) class IV heart failure. **RESULTS:** The 4-year cumulative primary event rate was 17.2% in the PCI group and 15.6% in the medical therapy group (hazard ratio for death, reinfarction, or heart failure in the PCI group as compared with the medical therapy group, 1.16; 95% confidence interval [CI], 0.92 to 1.45; P=0.20). Rates of myocardial reinfarction (fatal and nonfatal) were 7.0% and 5.3% in the two groups, respectively (hazard ratio, 1.36; 95% CI, 0.92 to 2.00; P=0.13). Rates of nonfatal reinfarction were 6.9% and 5.0%, respectively (hazard ratio, 1.44; 95% CI, 0.96 to 2.16; P=0.08); only six reinfarctions (0.6%) were related to assigned PCI procedures. Rates of NYHA class IV heart failure (4.4% vs. 4.5%) and death (9.1% vs. 9.4%) were similar. There was no interaction between treatment effect and any subgroup variable (age, sex, race or ethnic group, infarct-related artery, ejection fraction, diabetes, Killip class, and the time from myocardial infarction to randomization). **CONCLUSIONS:** 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 in stable patients with occlusion of the infarct-related artery 3 to 28 days after myocardial infarction. (ClinicalTrials.gov number, NCT00004562 [ClinicalTrials.gov].).

Bangalore, S., J. Wetterslev, et al. (2008). "**Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis.**" *Lancet* **372**(9654): 1962-1976.

Type of Question: Therapy **Beginner Meta-analysis.**

Teaching Notes: Good to teach heterogeneity

Abstract: **BACKGROUND:** American College of Cardiology and American Heart Association (ACC/AHA) guidelines on perioperative assessment recommend perioperative beta blockers for non-cardiac surgery, although results of some clinical trials seem not to support this recommendation. We aimed to critically review the evidence to assess the use of perioperative beta blockers in patients having non-cardiac surgery. **METHODS:** We searched Pubmed and Embase for randomised controlled trials investigating the use of beta blockers in non-cardiac surgery. We extracted data for 30-day all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, heart failure, and myocardial ischaemia, safety outcomes of perioperative bradycardia, hypotension, and bronchospasm. **FINDINGS:** 33 trials included 12 306 patients. beta blockers were not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality, or heart failure, but were associated with a decrease (odds ratio [OR] 0.65, 95% CI 0.54-0.79) in non-fatal myocardial infarction (number needed to treat [NNT] 63) and decrease (OR 0.36, 0.26-0.50) in myocardial ischaemia (NNT 16) at the expense of an increase (OR 2.01, 1.27-3.68) in non-fatal strokes (number needed to harm [NNH] 293). The beneficial effects were driven mainly by trials with high risk of bias. For the safety outcomes, beta blockers were associated with a high risk of perioperative bradycardia requiring treatment (NNH 22), and perioperative hypotension requiring treatment (NNH 17). We recorded no increased risk of bronchospasm. **INTERPRETATION:** Evidence does not support the use of beta-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery. The ACC/AHA guidelines committee should soften their advocacy for this intervention until conclusive evidence is available.

De, B. K., S. Gangopadhyay, et al. (2009). "**Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial.**" *World J Gastroenterol* **15**(13): 1613-1619.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: Good to teach NNT and ARR

Abstract: **AIM:** To compare the efficacy of pentoxifylline and prednisolone in the treatment of severe alcoholic hepatitis, and to evaluate the role of different liver function scores in predicting prognosis. **METHODS:** Sixty-eight patients with severe alcoholic hepatitis (Maddrey score > or = 32) received pentoxifylline (n = 34, group I) or prednisolone (n = 34, group II) for 28 d in a randomized double-blind controlled study, and subsequently in an open study (with a tapering dose of prednisolone) for a

total of 3 mo, and were followed up over a period of 12 mo. **RESULTS:** Twelve patients in group II died at the end of 3 mo in contrast to five patients in group I. The probability of dying at the end of 3 mo was higher in group II as compared to group I (35.29% vs 14.71%, $P = 0.04$; log rank test). Six patients in group II developed hepatorenal syndrome as compared to none in group I. Pentoxifylline was associated with a significantly lower model for end-stage liver disease (MELD) score at the end of 28 d of therapy (15.53 \pm 3.63 vs 17.78 \pm 4.56, $P = 0.04$). Higher baseline Maddrey score was associated with increased mortality. **CONCLUSION:** Reduced mortality, improved risk-benefit profile and renoprotective effects of pentoxifylline compared with prednisolone suggest that pentoxifylline is superior to prednisolone for treatment of severe alcoholic hepatitis.

Sirven, J. I., D. M. Wingerchuk, et al. (2004). "**Seizure prophylaxis in patients with brain tumors: a meta-analysis.**" *Mayo Clin Proc* 79(12): 1489-1494.

Type of Question: Therapy **Intermediate Meta-analysis.**

Teaching Notes: Good to teach creating your own forest plot

Abstract: **OBJECTIVE:** To assess whether antiepileptic drugs (AEDs) should be prescribed to patients with brain tumors who have no history of seizures. **METHODS:** We performed a meta-analysis of randomized controlled trials (1966-2004) that evaluated the efficacy of AED prophylaxis vs no treatment or placebo to prevent seizures in patients with brain tumors who had no history of epilepsy. Summary odds ratios (ORs) were calculated using a random-effects model. Three subanalyses were performed to assess pooled ORs of seizures in patients with primary glial tumors, cerebral metastases, and meningiomas. **RESULTS:** Of 474 articles found in the initial search, 17 were identified as primary studies. Five trials met inclusion criteria: patients with a neoplasm (primary glial tumors, cerebral metastases, and meningiomas) but no history of epilepsy who were randomized to either an AED or placebo. The 3 AEDs studied were phenobarbital, phenytoin, and valproic acid. Of the 5 trials, 4 showed no statistical benefit of seizure prophylaxis with an AED. Meta-analysis confirmed the lack of AED benefit at 1 week (OR, 0.91; 95% confidence interval [CI], 0.45-1.83) and at 6 months (OR, 1.01; 95% CI, 0.51-1.98) of follow-up. The AEDs had no effect on seizure prevention for specific tumor pathology, including primary glial tumors (OR, 3.46; 95% CI, 0.32-37.47), cerebral metastases (OR, 2.50; 95% CI, 0.25-24.72), and meningiomas (OR, 0.62; 95% CI, 0.10-3.85). **CONCLUSIONS:** No evidence supports AED prophylaxis with phenobarbital, phenytoin, or valproic acid in patients with brain tumors and no history of seizures, regardless of neoplastic type. Subspecialists who treat patients with brain tumors need more education on this issue. Future randomized controlled trials should address whether any of the newer AEDs are useful for seizure prophylaxis.

Salpeter, S. R., T. M. Ormiston, et al. (2004). "**Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis.**" *Chest* 125(6): 2309-2321.

Type of Question: Therapy **Beginner Meta-analysis.**

Teaching Notes: Good to teach surrogate outcomes

Abstract: **BACKGROUND:** beta-Adrenergic agonists exert physiologic effects that are the opposite of those of beta-blockers. beta-Blockers are known to reduce morbidity and mortality in patients with cardiac disease. beta(2)-Agonist use in patients with obstructive airway disease has been associated with an increased risk for myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death. **OBJECTIVES:** To assess the cardiovascular safety of beta(2)-agonist use in patients with obstructive airway disease, defined as asthma or COPD. **METHODS:** A meta-analysis of randomized placebo-controlled trials of beta(2)-agonist treatment in patients with obstructive airway disease was performed, to evaluate the short-term effect on heart rate and potassium concentrations, and the long-term effect on adverse cardiovascular events. Longer duration trials were included in the analysis if they reported at least one adverse event. Adverse events included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, or sudden death. **RESULTS:** Thirteen single-dose trials and 20 longer duration trials were included in the study. A single dose of beta(2)-agonist increased the heart rate by 9.12 beats/min (95% confidence interval [CI], 5.32 to 12.92) and reduced the potassium concentration by 0.36 mmol/L (95% CI, 0.18 to 0.54), compared to placebo. For trials lasting from 3 days to 1 year, beta(2)-agonist treatment significantly increased the risk for a cardiovascular event (relative risk [RR], 2.54; 95% CI, 1.59 to 4.05) compared to placebo. The RR

for sinus tachycardia alone was 3.06 (95% CI, 1.70 to 5.50), and for all other events it was 1.66 (95% CI, 0.76 to 3.6). **CONCLUSION:** beta(2)-Agonist use in patients with obstructive airway disease increases the risk for adverse cardiovascular events. The initiation of treatment increases heart rate and reduces potassium concentrations compared to placebo. It could be through these mechanisms, and other effects of beta-adrenergic stimulation, that beta(2)-agonists may precipitate ischemia, congestive heart failure, arrhythmias, and sudden death.

Becker, G., D. Galandi, et al. (2006). "**Malignant ascites: systematic review and guideline for treatment.**" *Eur J Cancer* **42**(5): 589-597.

Type of Question: Therapy **Systematic review.**

Teaching Notes: Good to teach difference between a meta-analysis and a systematic review

Abstract: A guideline on the management of symptomatic malignant ascites by abdominal paracentesis, diuretics and peritoneovenous shunting, based on a systematic review of the literature is presented. Thirty-two relevant studies were identified. None were randomized control trials, one was a non-randomized open controlled trial, five were cohort studies or prospective uncontrolled trials, 26 studies were non-analytic studies like case series. Although paracentesis, diuretics and shunting are commonly used procedures, the evidence is weak. Available data show good, although temporary effect of paracentesis on symptom relief. Fluid withdrawal speed and concurrent intravenous hydration is not sufficiently studied. Peritoneovenous shunts can control ascites in patients with malignant ascites, but have to be balanced by the potential risks of this procedure. The available data about diuretics in treatment of malignant ascites are controversial. The use of diuretics therefore should be considered in all patients, but has to be evaluated individually.

Saitz, R., M. F. Mayo-Smith, et al. (1994). "**Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial.**" *JAMA* **272**(7): 519-523.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Good to teach concealed allocation

Abstract: **OBJECTIVE--**To assess the effect of an individualized treatment regimen on the intensity and duration of medication treatment for alcohol withdrawal. **DESIGN--**A randomized double-blind, controlled trial. **SETTING--**An inpatient detoxification unit in a Veterans Affairs medical center. **PATIENTS--**One hundred one patients admitted for the treatment of alcohol withdrawal who could give informed consent and had no history of seizures or medication use that might alter the clinical course of withdrawal. **INTERVENTION--**Patients were randomized to either a standard course of chlordiazepoxide four times daily with additional medication as needed (fixed-schedule therapy) or to a treatment regimen that provided chlordiazepoxide only in response to the development of the signs and symptoms of alcohol withdrawal (symptom-triggered therapy). The need for administration of "as-needed" medication was determined using a validated measure of the severity of alcohol withdrawal. **MAIN OUTCOME MEASURES--**Duration of medication treatment and total chlordiazepoxide administered. **RESULTS--**The median duration of treatment in the symptom-triggered group was 9 hours, compared with 68 hours in the fixed-schedule group ($P < .001$). The symptom-triggered group received 100 mg of chlordiazepoxide, and the fixed-schedule group received 425 mg ($P < .001$). There were no significant differences in the severity of withdrawal during treatment or in the incidence of seizures or delirium tremens. **CONCLUSIONS--**Symptom-triggered therapy individualizes treatment, decreases both treatment duration and the amount of benzodiazepine used, and is as efficacious as standard fixed-schedule therapy for alcohol withdrawal.

Liu, Z., Z. Shi, et al. (2009). "**Carotid artery stenting versus carotid endarterectomy: systematic review and meta-analysis.**" *World J Surg* **33**(3): 586-596.

Type of Question: Therapy **Intermediate Meta-analysis.**

Teaching Notes: Good to teach heterogeneity

Abstract: **BACKGROUND:** The aim of this study was to evaluate and investigate the complications of carotid endarterectomy (CEA) and carotid artery stenting (CAS) by performing a meta-analysis based on prospective randomized controlled trials (RCTs). **METHODS:** We performed a search of multiple electronic databases for RCTs containing patients with carotid stenosis who underwent CAS or

CEA, focusing on studies published during 1995-2008. RESULTS: Eight trials with 2942 patients (1462 with CEA, 1480 with CAS) were analyzed. The pooled relative risk (RR) after CEA for stroke/death 30 days or 1 year was similar to that for CAS. Thirty-day RR = 0.69, 95% confidence interval (CI) = 0.45-1.07, $p = 0.10$. One-year RR = 0.88, 95% CI = 0.43-1.79, $p = 0.72$. The rates of death, disabling stroke, and nondisabling stroke at 30 days did not differ significantly between CEA and CAS in the subgroup analysis. Compared with CEA, the relative risk of disabling stroke/death within 30 days was not significantly less for CAS with embolic protection devices (EPDs). The relative risk of myocardial infarction within 30 days, myocardial infarction within 1 year, and cervical/peripheral nerve injury within 30 days were significantly higher after CEA; the relative risk of bradycardia/hypotension within 30 days and the 1-year restenosis rate were significantly higher after CAS. CONCLUSIONS: CAS is equal to CEA with regard to the incidence of stroke/death. These procedures may be considered complementary rather than competing modes of therapy, each of which can be optimized with careful patient selection. CAS with an EPD may be appropriate in certain patients, and in general CAS should be considered cautiously in symptomatic patients.

Halkes, P. H., J. van Gijn, et al. (2006). "Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial." *Lancet* 367(9523): 1665-1673.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Good to teach composite outcomes

Abstract: BACKGROUND: Results of trials of aspirin and dipyridamole combined versus aspirin alone for the secondary prevention of vascular events after ischaemic stroke of presumed arterial origin are inconsistent. Our aim was to resolve this uncertainty. METHODS: We did a randomised controlled trial in which we assigned patients to aspirin (30-325 mg daily) with ($n=1363$) or without ($n=1376$) dipyridamole (200 mg twice daily) within 6 months of a transient ischaemic attack or minor stroke of presumed arterial origin. Our primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first. Treatment was open, but auditing of outcome events was blinded. Primary analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial (number ISRCTN73824458) and with (NCT00161070). FINDINGS: Mean follow-up was 3.5 years (SD 2.0). Median aspirin dose was 75 mg in both treatment groups (range 30-325); extended-release dipyridamole was used by 83% ($n=1131$) of patients on the combination regimen. Primary outcome events arose in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone (hazard ratio 0.80, 95% CI 0.66-0.98; absolute risk reduction 1.0% per year, 95% CI 0.1-1.8). Addition of the ESPRIT data to the meta-analysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or myocardial infarction of 0.82 (95% CI 0.74-0.91). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs 184), mainly because of headache. INTERPRETATION: The ESPRIT results, combined with the results of previous trials, provide sufficient evidence to prefer the combination regimen of aspirin plus dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischaemia of arterial origin.

Abell, T., R. McCallum, et al. (2003). "Gastric electrical stimulation for medically refractory gastroparesis." *Gastroenterology* 125(2): 421-428.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Good to teach NNT/ARR

Abstract: BACKGROUND & AIMS: This study investigated the efficacy of gastric electrical stimulation for the treatment of symptomatic gastroparesis unresponsive to standard medical therapy. METHODS: Thirty-three patients with chronic gastroparesis (17 diabetic and 16 idiopathic) received continuous high-frequency/low-energy gastric electrical stimulation via electrodes in the muscle wall of the antrum connected to a neurostimulator in an abdominal wall pocket. After implantation, patients were randomized in a double-blind crossover design to stimulation ON or OFF for 1-month periods. The blind was then broken, and all patients were programmed to stimulation ON and evaluated at 6 and 12 months. Outcome measures were vomiting frequency, preference for ON or OFF, upper gastrointestinal tract symptoms, quality of life, gastric emptying, and adverse events. RESULTS: In the double-blind portion of the study, self-reported vomiting frequency was significantly reduced in the ON vs. OFF period ($P < 0.05$)

and this symptomatic improvement was consistent with the significant patient preference ($P < 0.05$) for the ON vs. OFF period determined before breaking the blind. In the unblinded portion of the study, vomiting frequency decreased significantly ($P < 0.05$) at 6 and 12 months. Scores for symptom severity and quality of life significantly improved ($P < 0.05$) at 6 and 12 months, whereas gastric emptying was only modestly accelerated. Five patients had their gastric electrical stimulation system explanted or revised because of infection or other complications. **CONCLUSIONS:** High-frequency/low-energy gastric electrical stimulation significantly decreased vomiting frequency and gastrointestinal symptoms and improved quality of life in patients with severe gastroparesis.

Fernandez, J., M. Navasa, et al. (2007). "**Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis.**" *Gastroenterology* 133(3): 818-824.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Good to teach NNT and ARR

Abstract: **BACKGROUND & AIMS:** Norfloxacin is highly effective in preventing spontaneous bacterial peritonitis recurrence in cirrhosis, but its role in the primary prevention of this complication is uncertain. **METHODS:** Patients with cirrhosis and low protein ascitic levels (<15 g/L) with advanced liver failure (Child-Pugh score ≥ 9 points with serum bilirubin level ≥ 3 mg/dL) or impaired renal function (serum creatinine level ≥ 1.2 mg/dL, blood urea nitrogen level ≥ 25 mg/dL, or serum sodium level ≤ 130 mEq/L) were included in a randomized controlled trial aimed at comparing norfloxacin (35 patients) vs placebo (33 patients) in the primary prophylaxis of spontaneous bacterial peritonitis. The main end points of the trial were 3-month and 1-year probability of survival. Secondary end points were 1-year probability of development of spontaneous bacterial peritonitis and hepatorenal syndrome. **RESULTS:** Norfloxacin administration reduced the 1-year probability of developing spontaneous bacterial peritonitis (7% vs 61%, $P < .001$) and hepatorenal syndrome (28% vs 41%, $P = .02$), and improved the 3-month (94% vs 62%, $P = .003$) and the 1-year (60% vs 48%, $P = .05$) probability of survival compared with placebo. **CONCLUSIONS:** Primary prophylaxis with norfloxacin has a great impact in the clinical course of patients with advanced cirrhosis. It reduces the incidence of spontaneous bacterial peritonitis, delays the development of hepatorenal syndrome, and improves survival.

Austin, M. A., K. E. Wills, et al. (2010). "**Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial.**" *BMJ* 341: c5462.

Type of Question: Therapy **RCT.**

Teaching Notes: COPD and titrated O₂: More and more studies of complex interventions will use a cluster randomized design. Savvy evidence consumers need to know the advantages and limitations of these kinds of studies and how to appraise them.

Abstract: **OBJECTIVES:** To compare standard high flow oxygen treatment with titrated oxygen treatment for patients with an acute exacerbation of chronic obstructive pulmonary disease in the prehospital setting. **DESIGN:** Cluster randomised controlled parallel group trial. **SETTING:** Ambulance service in Hobart, Tasmania, Australia. **PARTICIPANTS:** 405 patients with a presumed acute exacerbation of chronic obstructive pulmonary disease who were treated by paramedics, transported, and admitted to the Royal Hobart Hospital during the trial period; 214 had a diagnosis of chronic obstructive pulmonary disease confirmed by lung function tests in the previous five years. **INTERVENTIONS:** High flow oxygen treatment compared with titrated oxygen treatment in the prehospital (ambulance/paramedic) setting. **MAIN OUTCOME MEASURE:** Prehospital or in-hospital mortality. **RESULTS:** In an intention to treat analysis, the risk of death was significantly lower in the titrated oxygen arm compared with the high flow oxygen arm for all patients (high flow oxygen $n=226$; titrated oxygen $n=179$) and for the subgroup of patients with confirmed chronic obstructive pulmonary disease (high flow $n=117$; titrated $n=97$). Overall mortality was 9% (21 deaths) in the high flow oxygen arm compared with 4% (7 deaths) in the titrated oxygen arm; mortality in the subgroup with confirmed chronic obstructive pulmonary disease was 9% (11 deaths) in the high flow arm compared with 2% (2 deaths) in the titrated oxygen arm. Titrated oxygen treatment reduced mortality compared with high flow oxygen by 58% for all patients (relative risk 0.42, 95% confidence interval 0.20 to 0.89; $P=0.02$) and by 78% for the patients with confirmed chronic obstructive pulmonary disease (0.22, 0.05 to 0.91; $P=0.04$). Patients with chronic obstructive pulmonary

disease who received titrated oxygen according to the protocol were significantly less likely to have respiratory acidosis (mean difference in pH 0.12 (SE 0.05); $P=0.01$; $n=28$) or hypercapnia (mean difference in arterial carbon dioxide pressure -33.6 (16.3) mm Hg; $P=0.02$; $n=29$) than were patients who received high flow oxygen. **CONCLUSIONS:** Titrated oxygen treatment significantly reduced mortality, hypercapnia, and respiratory acidosis compared with high flow oxygen in acute exacerbations of chronic obstructive pulmonary disease. These results provide strong evidence to recommend the routine use of titrated oxygen treatment in patients with breathlessness and a history or clinical likelihood of chronic obstructive pulmonary disease in the prehospital setting. **TRIAL REGISTRATION:** Australian New Zealand Clinical Trials Register ACTRN12609000236291.

Sung, J. J., J. Y. Lau, et al. (2010). "**Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial.**" *Ann Intern Med* 152(1): 1-9.

Type of Question: Therapy **RCT.**

Teaching Notes: Very well reported trial on an increasingly relevant clinical question.

Excellent example of intention to treat methodology .

Can be used to do "therapy math": number needed to treat etc.

Abstract: **BACKGROUND:** It is uncertain whether aspirin therapy should be continued after endoscopic hemostatic therapy in patients who develop peptic ulcer bleeding while receiving low-dose aspirin. **OBJECTIVE:** To test that continuing aspirin therapy with proton-pump inhibitors after endoscopic control of ulcer bleeding was not inferior to stopping aspirin therapy, in terms of recurrent ulcer bleeding in adults with cardiovascular or cerebrovascular diseases. **DESIGN:** A parallel randomized, placebo-controlled noninferiority trial, in which both patients and clinicians were blinded to treatment assignment, was conducted from 2003 to 2006 by using computer-generated numbers in concealed envelopes. (ClinicalTrials.gov registration number: NCT00153725) **SETTING:** A tertiary endoscopy center. **PATIENTS:** Low-dose aspirin recipients with peptic ulcer bleeding. **INTERVENTION:** 78 patients received aspirin, 80 mg/d, and 78 received placebo for 8 weeks immediately after endoscopic therapy. All patients received a 72-hour infusion of pantoprazole followed by oral pantoprazole. All patients completed follow-up. **MEASUREMENTS:** The primary end point was recurrent ulcer bleeding within 30 days confirmed by endoscopy. Secondary end points were all-cause and specific-cause mortality in 8 weeks. **RESULTS:** 156 patients were included in an intention-to-treat analysis. Three patients withdrew from the trial before finishing follow-up. Recurrent ulcer bleeding within 30 days was 10.3% in the aspirin group and 5.4% in the placebo group (difference, 4.9 percentage points [95% CI, -3.6 to 13.4 percentage points]). Patients who received aspirin had lower all-cause mortality rates than patients who received placebo (1.3% vs. 12.9%; difference, 11.6 percentage points [CI, 3.7 to 19.5 percentage points]). Patients in the aspirin group had lower mortality rates attributable to cardiovascular, cerebrovascular, or gastrointestinal complications than patients in the placebo group (1.3% vs. 10.3%; difference, 9 percentage points [CI, 1.7 to 16.3 percentage points]). **LIMITATIONS:** The sample size is relatively small, and only low-dose aspirin, 80 mg, was used. Two patients with recurrent bleeding in the placebo group did not have further endoscopy. **CONCLUSION:** Among low-dose aspirin recipients who had peptic ulcer bleeding, continuous aspirin therapy may increase the risk for recurrent bleeding but potentially reduces mortality rates. Larger trials are needed to confirm these findings.

Gerstein, H. C., M. E. Miller, et al. (2008). "**Effects of intensive glucose lowering in type 2 diabetes.**" *N Engl J Med* 358(24): 2545-2559.

Type of Question: Therapy **RCT.**

Teaching Notes: Action to Control Cardiovascular Risk in Diabetes Study Group

Abstract: **BACKGROUND:** Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors. **METHODS:** In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was

a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up. **RESULTS:** At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; $P=0.16$). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; $P=0.04$). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group ($P<0.001$). **CONCLUSIONS:** As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

Umpierrez, G. E., K. Latif, et al. (2004). "**Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis.**" Am J Med 117(5): 291-296.

Type of Question: Therapy **Intermediate-Advanced RCT.**

Teaching Notes: Mainly good to teach about spin and confounders—industry funded trial in which two groups differ in many ways in addition to the difference in main intervention; Conclusion made by authors is not cleanly supported by the experimental design or the data; Allocation concealment is unclear;

This paper is really best for advanced learners who are eager to learn how to untangle issues that contribute to 'spin' in industry funded research

Abstract: **PURPOSE:** To compare the efficacy and safety of subcutaneous insulin lispro with that of a standard low-dose intravenous infusion protocol of regular insulin in patients with uncomplicated diabetic ketoacidosis. **METHODS:** In this prospective, randomized open trial, 20 patients treated with subcutaneous insulin lispro were managed in regular medicine wards ($n=10$) or an intermediate care unit ($n=10$), while 20 patients treated with the intravenous protocol were managed in the intensive care unit. Patients treated with subcutaneous lispro received an initial injection of 0.3 unit/kg followed by 0.1 unit/kg/h until correction of hyperglycemia (blood glucose levels <250 mg/dL), followed by 0.05 to 0.1 unit/kg/h until resolution of diabetic ketoacidosis ($\text{pH} > \text{or} = 7.3$, bicarbonate $> \text{or} = 18$ mEq/L). Patients treated with intravenous regular insulin received an initial bolus of 0.1 unit/kg, followed by an infusion of 0.1 unit/kg/h until correction of hyperglycemia, then 0.05 to 0.1 unit/kg/h until resolution of diabetic ketoacidosis. **RESULTS:** Mean (\pm SD) admission biochemical parameters in patients treated with subcutaneous lispro (glucose: 674 ± 154 mg/dL; bicarbonate: 9.2 ± 4 mEq/L; pH : 7.17 ± 0.10) were similar to values in patients treated with intravenous insulin (glucose: 611 ± 264 mg/dL; bicarbonate: 10.6 ± 4 mEq/L; pH : 7.19 ± 0.08). The duration of treatment until correction of hyperglycemia (7 ± 3 hours vs. 7 ± 2 hours) and resolution of ketoacidosis (10 ± 3 hours vs. 11 ± 4 hours) in patients treated with subcutaneous lispro was not different than in patients treated with intravenous regular insulin. There were no deaths in either group, and there were no differences in the length of hospital stay, amount of insulin until resolution of diabetic ketoacidosis, or in the rate of hypoglycemia between treatment groups. Treatment of diabetic ketoacidosis in the intensive care unit was associated with 39% higher hospitalization charges than was treatment with subcutaneous lispro in a non-intensive care setting ($\$14,429 \pm \5243 vs. $\$8801 \pm \5549 , $P < 0.01$). **CONCLUSION:** Treatment of adult patients who have uncomplicated diabetic ketoacidosis with subcutaneous lispro every hour in a non-intensive care setting may be safe and more cost-effective than treatment with intravenous regular insulin in the intensive care unit.

Baker, W. L., C. I. Coleman, et al. (2009). "**Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease.**" Ann Intern Med 151(12): 861-871.

Type of Question: Therapy **Beginner Systematic review.**

Teaching Notes: Well done meta-analysis; Nicely reported with transparent grading of evidence; Benefits nicely documented, but harms less so; Forest plots can be used to teach heterogeneity (Figure A. total mortality)

Abstract: BACKGROUND: Patients with ischemic heart disease and preserved ventricular function experience considerable morbidity and mortality despite standard medical therapy. PURPOSE: To compare benefits and harms of using angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARBs), or combination therapy in adults with stable ischemic heart disease and preserved ventricular function. DATA SOURCES: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (earliest date, July 2009) were searched without language restrictions. STUDY SELECTION: Two independent investigators screened citations for trials of at least 6 months' duration that compared ACE inhibitors, ARBs, or combination therapy with placebo or active control and reported any of several clinical outcomes. DATA EXTRACTION: Using standardized protocols, 2 independent investigators extracted information about study characteristics and rated the quality and strength of evidence. Disagreement was resolved by consensus. DATA SYNTHESIS: 41 studies met eligibility criteria. Moderate- to high-strength evidence (7 trials; 32 559 participants) showed that ACE inhibitors reduce the relative risk (RR) for total mortality (RR, 0.87 [95% CI, 0.81 to 0.94]) and nonfatal myocardial infarction (RR, 0.83 [CI, 0.73 to 0.94]) but increase the RR for syncope (RR, 1.24 [CI, 1.02 to 1.52]) and cough (RR, 1.67 [CI, 1.22 to 2.29]) compared with placebo. Low-strength evidence (1 trial; 5926 participants) suggested that ARBs reduce the RR for the composite end point of cardiovascular mortality, nonfatal myocardial infarction, or stroke (RR, 0.88 [CI, 0.77 to 1.00]) but not for the individual components. Moderate-strength evidence (1 trial; 25 620 participants) showed similar effects on total mortality (RR, 1.07 [CI, 0.98 to 1.16]) and myocardial infarction (RR, 1.08 [CI, 0.94 to 1.23]) but an increased risk for discontinuations because of hypotension ($P < 0.001$) and syncope ($P = 0.035$) with combination therapy compared with ACE inhibitors alone. LIMITATIONS: Many studies either did not assess or did not report harms in a systematic manner. Many studies did not adequately report benefits or harms by various patient subgroups. CONCLUSION: Adding an ACE inhibitor to standard medical therapy improves outcomes, including reduced risk for mortality and myocardial infarctions, in some patients with stable ischemic heart disease and preserved ventricular function. Less evidence supports a benefit of ARB therapy, and combination therapy seems no better than ACE inhibitor therapy alone and increases harms. PRIMARY FUNDING SOURCE: Agency for Healthcare Research and Quality.

Temel, J. S., J. A. Greer, et al. (2010). "Early palliative care for patients with metastatic non-small-cell lung cancer." *N Engl J Med* 363(8): 733-742.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: Systems intervention RCT of a different care paradigm; Nicely done methods and interesting findings; Can calculate NNT to prevent depression

Abstract: BACKGROUND: Patients with metastatic non-small-cell lung cancer have a substantial symptom burden and may receive aggressive care at the end of life. We examined the effect of introducing palliative care early after diagnosis on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease. METHODS: We randomly assigned patients with newly diagnosed metastatic non-small-cell lung cancer to receive either early palliative care integrated with standard oncologic care or standard oncologic care alone. Quality of life and mood were assessed at baseline and at 12 weeks with the use of the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale and the Hospital Anxiety and Depression Scale, respectively. The primary outcome was the change in the quality of life at 12 weeks. Data on end-of-life care were collected from electronic medical records. RESULTS: Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86% of the remaining patients) completed assessments. Patients assigned to early palliative care had a better quality of life than did patients assigned to standard care (mean score on the FACT-L scale [in which scores range from 0 to 136, with higher scores indicating better quality of life], 98.0 vs. 91.5; $P=0.03$). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs. 38%, $P=0.01$). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs. 54%, $P=0.05$), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, $P=0.02$). CONCLUSIONS: Among patients with metastatic non-small-cell lung cancer, early palliative care led to

significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival. (Funded by an American Society of Clinical Oncology Career Development Award and philanthropic gifts; ClinicalTrials.gov number, NCT01038271.)

De Berardis, G., M. Sacco, et al. (2009). "**Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials.**" *BMJ* 339: b4531.

Type of Question: Therapy **Beginner - Intermediate Meta-analysis.**

Teaching Notes: Beginner / Intermediate meta-analysis of aspirin for primary prevention in diabetics; Large number of patients, nice forest plots; Very good for teaching about heterogeneity and I-square

Abstract: **OBJECTIVE:** To evaluate the benefits and harms of low dose aspirin in people with diabetes and no cardiovascular disease. **DESIGN:** Meta-analysis of randomised controlled trials. **DATA SOURCES:** Medline (1966-November 2008), the Cochrane central register of controlled trials (Cochrane Library 2008;issue 4), and reference lists of retrieved articles. Review methods Randomised trials of aspirin compared with placebo or no aspirin in people with diabetes and no pre-existing cardiovascular disease were eligible for inclusion. Data on major cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and all cause mortality) were extracted and pooled with a random effect model. Results are reported as relative risks with 95% confidence intervals. **RESULTS:** Of 157 studies in the literature searches, six were eligible (10 117 participants). When aspirin was compared with placebo there was no statistically significant reduction in the risk of major cardiovascular events (five studies, 9584 participants; relative risk 0.90, 95% confidence interval 0.81 to 1.00), cardiovascular mortality (four studies, n=8557, 0.94; 0.72 to 1.23), or all cause mortality (four studies, n=8557; 0.93, 0.82 to 1.05). Significant heterogeneity was found in the analysis for myocardial infarction ($I^2=62.2\%$; $P=0.02$) and stroke ($I^2=52.5\%$; $P=0.08$). Aspirin significantly reduced the risk of myocardial infarction in men (0.57, 0.34 to 0.94) but not in women (1.08, 0.71 to 1.65; P for interaction=0.056). Evidence relating to harms was inconsistent. **CONCLUSIONS:** A clear benefit of aspirin in the primary prevention of major cardiovascular events in people with diabetes remains unproved. Sex may be an important effect modifier. Toxicity is to be explored further.

Salpeter, S. R., A. J. Wall, et al. (2010). "**Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events.**" *Am J Med* 123(4): 322-328 e322.

Type of Question: Therapy **Beginner - Intermediate Meta-analysis.**

Teaching Notes: controversial topic; RCTs are summarized with outcome of increased risk (harm as opposed to the usual framework of looking for benefit); Good to discuss ethics (the RCTs were done to show benefit, but didn't end up showing that in all cases...); Nice Forest plots including use of I-squared; Article accompanied by an ACP-JC

Abstract: **BACKGROUND:** It is unclear whether long-acting beta-agonists with concomitant inhaled corticosteroids increase asthma-related intubations and deaths. We pooled data on long-acting beta-agonists with variable and concomitant inhaled corticosteroids to evaluate the risk for catastrophic asthma events. **METHODS:** We conducted searches of electronic databases, the US Food and Drug Administration website, clinical-trials registries, and selected references through December 2008. We analyzed randomized controlled trials in patients with asthma, which lasted at least 3 months, evaluated long-acting beta-agonists compared with placebo or long-acting beta-agonists with inhaled corticosteroids compared with corticosteroids alone, and included at least 1 catastrophic event, defined as asthma-related intubation or death. **RESULTS:** In pooled trial data that included 36,588 participants, long-acting beta-agonists increased catastrophic events 2-fold (Peto odds ratio [OR] 2.10; 95% confidence interval [CI], 1.37-3.22). Statistically significant increases were seen for long-acting beta-agonists with variable corticosteroids compared with placebo (OR 1.83; 95% CI, 1.14-2.95) and for concomitant treatment with corticosteroids compared with corticosteroids alone (OR 3.65; 95% CI, 1.39-9.55). Similar increases in risk were seen for variable and concomitant corticosteroid use, salmeterol and formoterol, and children and adults. When the analysis was restricted to trials with controlled corticosteroid use, given as part of the study intervention, concomitant treatment still increased catastrophic events compared with corticosteroids alone (OR 8.19; 95% CI, 1.10-61.18). **CONCLUSION:** Long-acting beta-agonists increase

the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids.

Ray, K. K., S. R. Seshasai, et al. (2010). "**Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants.**" Arch Intern Med **170**(12): 1024-1031.

Type of Question: Therapy **Beginner Meta-analysis.**

Teaching Notes: Well done large meta-analysis of the use of statins for primary prevention in high risk patients without cardiac events. Beginner for a meta-analysis in that it has a manageable amount of data presented, forest plots are straightforward with reporting of I-squared

Abstract: BACKGROUND: Statins have been shown to reduce the risk of all-cause mortality among individuals with clinical history of coronary heart disease. However, it remains uncertain whether statins have similar mortality benefit in a high-risk primary prevention setting. Notably, all systematic reviews to date included trials that in part incorporated participants with prior cardiovascular disease (CVD) at baseline. Our objective was to reliably determine if statin therapy reduces all-cause mortality among intermediate to high-risk individuals without a history of CVD. DATA SOURCES: Trials were identified through computerized literature searches of MEDLINE and Cochrane databases (January 1970-May 2009) using terms related to statins, clinical trials, and cardiovascular end points and through bibliographies of retrieved studies. STUDY SELECTION: Prospective, randomized controlled trials of statin therapy performed in individuals free from CVD at baseline and that reported details, or could supply data, on all-cause mortality. DATA EXTRACTION: Relevant data including the number of patients randomized, mean duration of follow-up, and the number of incident deaths were obtained from the principal publication or by correspondence with the investigators. DATA SYNTHESIS: Data were combined from 11 studies and effect estimates were pooled using a random-effects model meta-analysis, with heterogeneity assessed with the I^2 statistic. Data were available on 65,229 participants followed for approximately 244,000 person-years, during which 2793 deaths occurred. The use of statins in this high-risk primary prevention setting was not associated with a statistically significant reduction (risk ratio, 0.91; 95% confidence interval, 0.83-1.01) in the risk of all-cause mortality. There was no statistical evidence of heterogeneity among studies ($I^2 = 23\%$; 95% confidence interval, 0%-61% [$P = .23$]). CONCLUSION: This literature-based meta-analysis did not find evidence for the benefit of statin therapy on all-cause mortality in a high-risk primary prevention set-up.

Van Gelder, I. C., H. F. Groenveld, et al. (2010). "**Lenient versus strict rate control in patients with atrial fibrillation.**" N Engl J Med **362**(15): 1363-1373.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: Intermediate RCT studying treatment paradigm of strict versus lenient control for atrial fibrillation; Well designed study but with several topics worthy of discussion including composite outcomes. Very good for discussion of application of evidence – strict control was not reached in a significant portion of the group randomized to that arm. How does that effect interpretation? Article has an ACP-JC summary which can help teachers prepare to teach the paper and also illustrate how quick and useful such summaries can be.

Abstract: BACKGROUND: Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation. METHODS: We randomly assigned 614 patients with permanent atrial fibrillation to undergo a lenient rate-control strategy (resting heart rate <110 beats per minute) or a strict rate-control strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of follow-up was at least 2 years, with a maximum of 3 years. RESULTS: The estimated cumulative incidence of the primary outcome at 3 years was 12.9% in the lenient-control group and 14.9% in the strict-control group, with an absolute difference with respect to the lenient-control group of -2.0 percentage points (90% confidence interval, -7.6 to 3.5; $P < 0.001$ for the prespecified noninferiority margin). The frequencies of the components of the primary outcome were

similar in the two groups. More patients in the lenient-control group met the heart-rate target or targets (304 [97.7%], vs. 203 [67.0%] in the strict-control group; $P < 0.001$) with fewer total visits (75 [median, 0], vs. 684 [median, 2]; $P < 0.001$). The frequencies of symptoms and adverse events were similar in the two groups. **CONCLUSIONS:** In patients with permanent atrial fibrillation, lenient rate control is as effective as strict rate control and is easier to achieve. (ClinicalTrials.gov number, NCT00392613.)

Chastre, J., M. Wolff, et al. (2003). "**Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial.**" *JAMA* 290(19): 2588-2598.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: Noninferiority Trial; Good methods for discussion of RCT including blinding, allocation concealment—the trial was blinded for the first 8 days of the study and then antibiotics continued or not continued by random assignment from days 9 through 15. Given the study question and patient population it is a nice study design. Not necessarily for beginners, but for more advanced learners this is a nice study about an important topic (duration of therapy). Can calculate NNH for superinfection / relapse from Table 4

Abstract: **CONTEXT:** The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU). **OBJECTIVE:** To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective, randomized, double-blind (until day 8) clinical trial conducted in 51 French ICUs. A total of 401 patients diagnosed as having developed VAP by quantitative culture results of bronchoscopic specimens and who had received initial appropriate empirical antimicrobial therapy were enrolled between May 1999 and June 2002. **INTERVENTION:** A total of 197 patients were randomly assigned to receive 8 days and 204 to receive 15 days of therapy with an antibiotic regimen selected by the treating physician. **MAIN OUTCOME MEASURES:** Primary outcome measures—death from any cause, microbiologically documented pulmonary infection recurrence, and antibiotic-free days—were assessed 28 days after VAP onset and analyzed on an intent-to-treat basis. **RESULTS:** Compared with patients treated for 15 days, those treated for 8 days had neither excess mortality (18.8% vs 17.2%; difference, 1.6%; 90% confidence interval [CI], -3.7% to 6.9%) nor more recurrent infections (28.9% vs 26.0%; difference, 2.9%; 90% CI, -3.2% to 9.1%), but they had more mean (SD) antibiotic-free days (13.1 [7.4] vs 8.7 [5.2] days, $P < .001$). The number of mechanical ventilation-free days, the number of organ failure-free days, the length of ICU stay, and mortality rates on day 60 for the 2 groups did not differ. Although patients with VAP caused by nonfermenting gram-negative bacilli, including *Pseudomonas aeruginosa*, did not have more unfavorable outcomes when antimicrobial therapy lasted only 8 days, they did have a higher pulmonary infection-recurrence rate compared with those receiving 15 days of treatment (40.6% vs 25.4%; difference, 15.2%, 90% CI, 3.9%-26.6%). Among patients who developed recurrent infections, multiresistant pathogens emerged less frequently in those who had received 8 days of antibiotics (42.1% vs 62.0% of pulmonary recurrences, $P = .04$). **CONCLUSIONS:** Among patients who had received appropriate initial empirical therapy, with the possible exception of those developing nonfermenting gram-negative bacillus infections, comparable clinical effectiveness against VAP was obtained with the 8- and 15-day treatment regimens. The 8-day group had less antibiotic use.

Buse, J. B., R. M. Bergenstal, et al. (2011). "**Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial.**" *Ann Intern Med* 154(2): 103-112.

Type of Question: Therapy **Intermediate RCT.**

Teaching Notes: Nicely reported methods and a fairly straightforward RCT, however good example of article with a lot of spin / industry bias including faulty comparator
The paper seems to be written to obtain FDA approval, rather than to answer a patient-driven scientific question. Teaching points include good example of why we should read the methods / results and draw our own conclusions.

Abstract: **BACKGROUND:** Insulin replacement in diabetes often requires prandial intervention to reach hemoglobin A(c) (HbA(c)) targets. **OBJECTIVE:** To test whether twice-daily exenatide injections reduce HbA(c) levels more than placebo in people receiving insulin glargine. **DESIGN:** Parallel,

randomized, placebo-controlled trial, blocked and stratified by HbA(c) level at site, performed from October 2008 to January 2010. Participants, investigators, and personnel conducting the study were masked to treatment assignments. (ClinicalTrials.gov registration number: NCT00765817) SETTING: 59 centers in 5 countries. PATIENTS: Adults with type 2 diabetes and an HbA(c) level of 7.1% to 10.5% who were receiving insulin glargine alone or in combination with metformin or pioglitazone (or both agents). INTERVENTION: Assignment by a centralized, computer-generated, random-sequence interactive voice-response system to exenatide, 10 microg twice daily, or placebo for 30 weeks. MEASUREMENTS: The primary outcome was change in HbA(c) level. Secondary outcomes included the percentage of participants with HbA(c) values of 7.0% or less and 6.5% or less, 7-point self-monitored glucose profiles, body weight, waist circumference, insulin dose, hypoglycemia, and adverse events. RESULTS: 112 of 138 exenatide recipients and 101 of 123 placebo recipients completed the study. The HbA(c) level decreased by 1.74% with exenatide and 1.04% with placebo (between-group difference, -0.69% [95% CI, -0.93% to -0.46%]; $P < 0.001$). Weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo (between-group difference, -2.7 kg [CI, -3.7 to -1.7]). Average increases in insulin dosage with exenatide and placebo were 13 U/d and 20 U/d. The estimated rate of minor hypoglycemia was similar between groups. Thirteen exenatide recipients and 1 placebo recipient discontinued the study because of adverse events ($P < 0.010$); rates of nausea (41% vs. 8%), diarrhea (18% vs. 8%), vomiting (18% vs. 4%), headache (14% vs. 4%), and constipation (10% vs. 2%) were higher with exenatide than with placebo. LIMITATIONS: The study was of short duration. There were slight imbalances between groups at baseline in terms of sex, use of concomitant glucose-lowering medications, and HbA(c) levels, and more exenatide recipients than placebo recipients withdrew because of adverse events. CONCLUSION: Adding twice-daily exenatide injections improved glycemic control without increased hypoglycemia or weight gain in participants with uncontrolled type 2 diabetes who were receiving insulin glargine treatment. Adverse events of exenatide included nausea, diarrhea, vomiting, headache, and constipation. PRIMARY FUNDING SOURCE: Alliance of Eli Lilly and Company and Amylin Pharmaceuticals.

Bruckert, E., J. Labreuche, et al. (2010). "Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis." *Atherosclerosis* 210(2): 353-361.

Type of Question: Therapy **intermediate meta-analysis.**

Teaching Notes: The title sounds impressive but there are all sorts of problems with it --- too broad a question, pooling with too much clinical & statistical heterogeneity, and weird use of OR. I would say this is a more difficult paper to use in groups who already understand the basics of what to look for.

Abstract: OBJECTIVE: High-density lipoprotein cholesterol (HDL-C) concentration is a strong predictor of cardiovascular events in both naive and statin-treated patients. Nicotinic acid is an attractive option for decreasing residual risk in statin-treated or statin-intolerant patients since it increases HDL-C by up to 20% and decreases low-density lipoprotein cholesterol and lipoprotein(a) plasma concentrations. METHODS: We performed a computerized PubMed literature search that focused on clinical trials evaluating niacin, alone or in combination with other lipid-lowering drugs, published between January 1966 and August 2008. RESULTS: Among 587 citations, 29 full articles were read and 14 were eligible for inclusion. Overall 11 randomized controlled trials enrolled 2682 patients in the active group and 3934 in the control group. In primary analysis, niacin significantly reduced major coronary events (relative odds reduction=25%, 95% CI 13, 35), stroke (26%, 95% CI=8, 41) and any cardiovascular events (27%, 95% CI=15, 37). Except for stroke, the pooled between-group difference remained significant in sensitivity analysis excluding the largest trial. In comparison with the non-niacin group, more patients in the niacin group had regression of coronary atherosclerosis (relative increase=92%, 95% CI=39, 67) whereas the rate of patients with progression decreased by 41%, 95% CI=25, 53. Similar effects of niacin were found on carotid intima thickness with a weighted mean difference in annual change of -17 microm/year (95% CI=-22, -12). CONCLUSIONS: Although the studies were conducted before statin therapy became standard care, and mostly in patients in secondary prevention, with various dosages of nicotinic acid 1-3g/day, this meta-analysis found positive effects of niacin alone or in combination on all cardiovascular events and on atherosclerosis evolution.

Olasveengen, T. M., K. Sunde, et al. (2009). "Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial." *JAMA* 302(20): 2222-2229.

Type of Question: Therapy **Beginner - Intermediate RCT.**

Teaching Notes: Controversial topic- good ethics discussion about ethics of randomization; Very good for discussion of allocation concealment and intention to treat analysis
Not good for teaching therapy math because there are no numbers amenable for NNT or NNH calculation

Abstract: CONTEXT: Intravenous access and drug administration are included in advanced cardiac life support (ACLS) guidelines despite a lack of evidence for improved outcomes. Epinephrine was an independent predictor of poor outcome in a large epidemiological study, possibly due to toxicity of the drug or cardiopulmonary resuscitation (CPR) interruptions secondary to establishing an intravenous line and drug administration. OBJECTIVE: To determine whether removing intravenous drug administration from an ACLS protocol would improve survival to hospital discharge after out-of-hospital cardiac arrest. DESIGN, SETTING, AND PATIENTS: Prospective, randomized controlled trial of consecutive adult patients with out-of-hospital nontraumatic cardiac arrest treated within the emergency medical service system in Oslo, Norway, between May 1, 2003, and April 28, 2008. INTERVENTIONS: Advanced cardiac life support with intravenous drug administration or ACLS without access to intravenous drug administration. MAIN OUTCOME MEASURES: The primary outcome was survival to hospital discharge. The secondary outcomes were 1-year survival, survival with favorable neurological outcome, hospital admission with return of spontaneous circulation, and quality of CPR (chest compression rate, pauses, and ventilation rate). RESULTS: Of 1183 patients for whom resuscitation was attempted, 851 were included; 418 patients were in the ACLS with intravenous drug administration group and 433 were in the ACLS with no access to intravenous drug administration group. The rate of survival to hospital discharge was 10.5% for the intravenous drug administration group and 9.2% for the no intravenous drug administration group ($P = .61$), 32% vs 21%, respectively, ($P < .001$) for hospital admission with return of spontaneous circulation, 9.8% vs 8.1% ($P = .45$) for survival with favorable neurological outcome, and 10% vs 8% ($P = .53$) for survival at 1 year. The quality of CPR was comparable and within guideline recommendations for both groups. After adjustment for ventricular fibrillation, response interval, witnessed arrest, or arrest in a public location, there was no significant difference in survival to hospital discharge for the intravenous group vs the no intravenous group (adjusted odds ratio, 1.15; 95% confidence interval, 0.69-1.91). CONCLUSION: Compared with patients who received ACLS without intravenous drug administration following out-of-hospital cardiac arrest, patients with intravenous access and drug administration had higher rates of short-term survival with no statistically significant improvement in survival to hospital discharge, quality of CPR, or long-term survival. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00121524.

Giuliano, A. E., K. K. Hunt, et al. (2011). "Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial." *JAMA* 305(6): 569-575.

Type of Question: Therapy **Intermediate - Advanced RCT.**

Teaching Notes: This is a well done RCT overall, could be useful as a therapy article, but it's strength as a teaching article is in the non-inferiority design, and the pitfalls of non-inferiority when you don't see the number of outcomes you planned for. Intermediate to advanced

Abstract: CONTEXT: Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival. OBJECTIVE: To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer. DESIGN, SETTING, AND PATIENTS: The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected. INTERVENTIONS: All patients underwent lumpectomy and tangential whole-breast irradiation. Those with SLN metastases identified by SLND were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of 10 or more nodes. Systemic therapy was at the discretion of the treating physician. MAIN

OUTCOME MEASURES: Overall survival was the primary end point, with a noninferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is noninferior to ALND. Disease-free survival was a secondary end point. **RESULTS:** Clinical and tumor characteristics were similar between 445 patients randomized to ALND and 446 randomized to SLND alone. However, the median number of nodes removed was 17 with ALND and 2 with SLND alone. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%-94.5%) with ALND and 92.5% (95% CI, 90.0%-95.1%) with SLND alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%-86.3%) with ALND and 83.9% (95% CI, 80.2%-87.9%) with SLND alone. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56-1.11) without adjustment and 0.87 (90% CI, 0.62-1.23) after adjusting for age and adjuvant therapy. **CONCLUSION:** Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00003855.

Chan, F. K., A. Lanas, et al. (2010). "**Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial.**" *Lancet* 376(9736): 173-179.

Type of Question: Therapy **Beginner - Intermediate RCT.**

Teaching Notes: A therapy article which can be useful for basic therapy validity and calculating ARR, RRR, NNT. Also raises the issue of the composite outcome, and which components of the composite drive the results. Can be beginner to intermediate.

Abstract: **BACKGROUND:** Cyclo-oxygenase (COX)-2-selective non-steroidal anti-inflammatory drugs (NSAIDs) and non-selective NSAIDs plus a proton-pump inhibitor (PPI) have similar upper gastrointestinal outcomes, but risk of clinical outcomes across the entire gastrointestinal tract might be lower with selective drugs than with non-selective drugs. We aimed to compare risk of gastrointestinal events associated with celecoxib versus diclofenac slow release plus omeprazole. **METHODS:** We undertook a 6-month, double-blind, randomised trial in patients with osteoarthritis or rheumatoid arthritis at increased gastrointestinal risk at 196 centres in 32 countries or territories. Patients tested negative for *Helicobacter pylori* and were aged 60 years and older or 18 years and older with previous gastroduodenal ulceration. We used a computer-generated randomisation schedule to assign patients in a 1:1 ratio to receive celecoxib 200 mg twice a day or diclofenac slow release 75 mg twice a day plus omeprazole 20 mg once a day. Patients and investigators were masked to treatment allocation. The primary endpoint was a composite of clinically significant upper or lower gastrointestinal events adjudicated by an independent committee. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00141102. **FINDINGS:** 4484 patients were randomly allocated to treatment (2238 celecoxib; 2246 diclofenac plus omeprazole) and were included in intention-to-treat analyses. 20 (0.9%) patients receiving celecoxib and 81 (3.8%) receiving diclofenac plus omeprazole met criteria for the primary endpoint (hazard ratio 4.3, 95% CI 2.6-7.0; $p < 0.0001$). 114 (6%) patients taking celecoxib versus 167 (8%) taking diclofenac plus omeprazole withdrew early because of gastrointestinal adverse events ($p = 0.0006$). **INTERPRETATION:** Risk of clinical outcomes throughout the gastrointestinal tract was lower in patients treated with a COX-2-selective NSAID than in those receiving a non-selective NSAID plus a PPI. These findings should encourage review of approaches to reduce risk of NSAID treatment. **FUNDING:** Pfizer Inc.

Granger, C. B., J. H. Alexander, et al. (2011). "**Apixaban versus warfarin in patients with atrial fibrillation.**" *N Engl J Med* 365(11): 981-992.

Type of Question: Therapy **Advanced RCT.**

Teaching Notes: noninferiority with Apixaban for Afib - outstanding non-inferiority paper to review NI margins, methodology, assumptions

Abstract: **BACKGROUND:** Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin. **METHODS:** In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or

systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause. **RESULTS:** The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; $P < 0.001$), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; $P = 0.047$). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; $P < 0.001$), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; $P = 0.42$). **CONCLUSIONS:** In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.).

Carlberg, B., O. Samuelsson, et al. (2004). "Atenolol in hypertension: is it a wise choice?" *Lancet* 364(9446): 1684-1689.

Type of Question: Therapy **Beginner Meta-analysis.**

Teaching Notes: This is a nice straightforward meta-analysis that shows how a commonly used drug may not end up providing as much clinical benefit as originally thought. Can also be used to discuss how a surrogate end-point (blood pressure) does not always reflect the true impact on clinical events.

Abstract: **BACKGROUND:** Atenolol is one of the most widely used beta blockers clinically, and has often been used as a reference drug in randomised controlled trials of hypertension. However, questions have been raised about atenolol as the best reference drug for comparisons with other antihypertensives. Thus, our aim was to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients. **METHODS:** Reports were identified through searches of The Cochrane Library, MEDLINE, relevant textbooks, and by personal communication with established researchers in hypertension. Randomised controlled trials that assessed the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension were included. **FINDINGS:** We identified four studies that compared atenolol with placebo or no treatment, and five that compared atenolol with other antihypertensive drugs. Despite major differences in blood pressure lowering, there were no outcome differences between atenolol and placebo in the four studies, comprising 6825 patients, who were followed up for a mean of 4.6 years on all-cause mortality (relative risk 1.01 [95% CI 0.89-1.15]), cardiovascular mortality (0.99 [0.83-1.18]), or myocardial infarction (0.99 [0.83-1.19]). The risk of stroke, however, tended to be lower in the atenolol than in the placebo group (0.85 [0.72-1.01]). When atenolol was compared with other antihypertensives, there were no major differences in blood pressure lowering between the treatment arms. Our meta-analysis showed a significantly higher mortality (1.13 [1.02-1.25]) with atenolol treatment than with other active treatment, in the five studies comprising 17671 patients who were followed up for a mean of 4.6 years. Moreover, cardiovascular mortality also tended to be higher with atenolol treatment than with other antihypertensive treatment. Stroke was also more frequent with atenolol treatment. **INTERPRETATION:** Our results cast doubts on atenolol as a suitable drug for hypertensive patients. Moreover, they challenge the use of atenolol as a reference drug in outcome trials in hypertension.

(1987). "Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group." *N Engl J Med* 316(23): 1429-1435.

Type of Question: Therapy **RCT.**

Teaching Notes: This article has some historical significance in that it's the first demonstration of mortality benefit in heart failure with ACE inhibitors, and I like using it partly for that reason, as I think learners should have some idea about "landmark" papers. More significantly however, this is a great article for calculating number needed to treat (which ends up being very low) and then discussing why the number needed to treat is so low. In this study, the mortality was so high (because there was little other

effective therapy and because the patients had such severe heart failure) that the intervention had a major impact, leading to such a low number needed to treat. Whenever I use this article, I usually then ask the group to tell me why we have to treat many more patients in current practice with ACE inhibitors to prevent one death, and it's because the underlying mortality of the condition has changed with other therapies now available.

Abstract: To evaluate the influence of the angiotensin-converting-enzyme inhibitor enalapril (2.5 to 40 mg per day) on the prognosis of severe congestive heart failure (New York Heart Association [NYHA] functional class IV), we randomly assigned 253 patients in a double-blind study to receive either placebo (n = 126) or enalapril (n = 127). Conventional treatment for heart failure, including the use of other vasodilators, was continued in both groups. Follow-up averaged 188 days (range, 1 day to 20 months). The crude mortality at the end of six months (primary end point) was 26 percent in the enalapril group and 44 percent in the placebo group--a reduction of 40 percent (P = 0.002). Mortality was reduced by 31 percent at one year (P = 0.001). By the end of the study, there had been 68 deaths in the placebo group and 50 in the enalapril group--a reduction of 27 percent (P = 0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50 percent), whereas no difference was seen in the incidence of sudden cardiac death. A significant improvement in NYHA classification was observed in the enalapril group, together with a reduction in heart size and a reduced requirement for other medication for heart failure. The overall withdrawal rate was similar in both groups, but hypotension requiring withdrawal occurred in seven patients in the enalapril group and in no patients in the placebo group. After the initial dose of enalapril was reduced to 2.5 mg daily in high-risk patients, this side effect was less frequent. We conclude that the addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms. The beneficial effect on mortality is due to a reduction in death from the progression of heart failure.

Maitland, K., S. Kiguli, et al. (2011). "**Mortality after fluid bolus in African children with severe infection.**" *N Engl J Med* **364**(26): 2483-2495.

Type of Question: Therapy **RCT.**

Teaching Notes: I just used this paper for the Capstone EBM course, and it seemed to work well as a teaching paper. Good methods. Doesn't have blinding, but that leads to good discussion about situations when you can't blind. Also, there were worse outcomes in the intervention group, so you end up calculating a RRI and NNH. The results of this paper go against standard practice, so it generates good discussion of why that might have occurred.

Abstract: **BACKGROUND:** The role of fluid resuscitation in the treatment of children with shock and life-threatening infections who live in resource-limited settings is not established. **METHODS:** We randomly assigned children with severe febrile illness and impaired perfusion to receive boluses of 20 to 40 ml of 5% albumin solution (albumin-bolus group) or 0.9% saline solution (saline-bolus group) per kilogram of body weight or no bolus (control group) at the time of admission to a hospital in Uganda, Kenya, or Tanzania (stratum A); children with severe hypotension were randomly assigned to one of the bolus groups only (stratum B). All children received appropriate antimicrobial treatment, intravenous maintenance fluids, and supportive care, according to guidelines. Children with malnutrition or gastroenteritis were excluded. The primary end point was 48-hour mortality; secondary end points included pulmonary edema, increased intracranial pressure, and mortality or neurologic sequelae at 4 weeks. **RESULTS:** The data and safety monitoring committee recommended halting recruitment after 3141 of the projected 3600 children in stratum A were enrolled. Malaria status (57% overall) and clinical severity were similar across groups. The 48-hour mortality was 10.6% (111 of 1050 children), 10.5% (110 of 1047 children), and 7.3% (76 of 1044 children) in the albumin-bolus, saline-bolus, and control groups, respectively (relative risk for saline bolus vs. control, 1.44; 95% confidence interval [CI], 1.09 to 1.90; P=0.01; relative risk for albumin bolus vs. saline bolus, 1.01; 95% CI, 0.78 to 1.29; P=0.96; and relative risk for any bolus vs. control, 1.45; 95% CI, 1.13 to 1.86; P=0.003). The 4-week mortality was 12.2%, 12.0%, and 8.7% in the three groups, respectively (P=0.004 for the comparison of bolus with control). Neurologic sequelae occurred in 2.2%, 1.9%, and 2.0% of the children in the respective groups (P=0.92), and pulmonary edema or increased intracranial pressure occurred in 2.6%, 2.2%, and 1.7% (P=0.17), respectively. In stratum B, 69% of the children (9 of 13) in the albumin-bolus group and 56% (9 of 16) in the saline-bolus group died (P=0.45). The results were consistent across centers and across subgroups according to the severity of shock and status with respect to malaria, coma, sepsis, acidosis, and severe

anemia. **CONCLUSIONS:** Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in these resource-limited settings in Africa. (Funded by the Medical Research Council, United Kingdom; FEAST Current Controlled Trials number, ISRCTN69856593.).

Boden, W. E., J. L. Probstfield, et al. (2011). "**Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy.**" *N Engl J Med* **365**(24): 2255-2267.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: AIM-HIGH trial, negative niacin trial - great for teaching about composite outcomes; trials stopped early and loss of power; surrogate outcomes (HDL vs. clinical outcomes).

Abstract: **BACKGROUND:** In patients with established cardiovascular disease, residual cardiovascular risk persists despite the achievement of target low-density lipoprotein (LDL) cholesterol levels with statin therapy. It is unclear whether extended-release niacin added to simvastatin to raise low levels of high-density lipoprotein (HDL) cholesterol is superior to simvastatin alone in reducing such residual risk. **METHODS:** We randomly assigned eligible patients to receive extended-release niacin, 1500 to 2000 mg per day, or matching placebo. All patients received simvastatin, 40 to 80 mg per day, plus ezetimibe, 10 mg per day, if needed, to maintain an LDL cholesterol level of 40 to 80 mg per deciliter (1.03 to 2.07 mmol per liter). The primary end point was the first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. **RESULTS:** A total of 3414 patients were randomly assigned to receive niacin (1718) or placebo (1696). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL cholesterol level from 35 mg per deciliter (0.91 mmol per liter) to 42 mg per deciliter (1.08 mmol per liter), lowered the triglyceride level from 164 mg per deciliter (1.85 mmol per liter) to 122 mg per deciliter (1.38 mmol per liter), and lowered the LDL cholesterol level from 74 mg per deciliter (1.91 mmol per liter) to 62 mg per deciliter (1.60 mmol per liter). The primary end point occurred in 282 patients in the niacin group (16.4%) and in 274 patients in the placebo group (16.2%) (hazard ratio, 1.02; 95% confidence interval, 0.87 to 1.21; $P=0.79$ by the log-rank test). **CONCLUSIONS:** Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels. (Funded by the National Heart, Lung, and Blood Institute and Abbott Laboratories; AIM-HIGH ClinicalTrials.gov number, NCT00120289.).

Phung, O. J., S. R. Kahn, et al. (2011). "**Dosing frequency of unfractionated heparin thromboprophylaxis: a meta-analysis.**" *Chest* **140**(2): 374-381.

Type of Question: Therapy **Beginner Meta-analysis.**

Teaching Notes: Phung, Olivia J

Abstract: **BACKGROUND:** In medical patients, it is unclear whether thromboprophylaxis with low-dose unfractionated heparin (UFH) should be administered bid or tid. **METHODS:** This study was a mixed-treatment comparison meta-analysis of randomized control trials that enrolled hospitalized nonsurgical patients at risk for VTE and compared UFH bid, UFH tid, or low-molecular-weight heparin (LMWH) to one another or to an inactive control subject. DVT, pulmonary embolism (PE), major bleeding, and death were measured. A Bayesian framework using a random-effects model was applied. **RESULTS:** Sixteen trials with moderate methodologic quality enrolling 27,667 patients contributed to this analysis. The relative risk and 95% credible intervals comparing UFH tid to UFH bid for DVT, PE, death, and major bleeding were 1.56 (0.64-4.33), 1.67 (0.49-208.09), 1.17 (0.72-1.95), and 0.89 (0.08-7.05), respectively. When compared with either dose of UFH, the use of LMWH has an effect similar to UFH on all four outcomes. **CONCLUSIONS:** Moderate-quality evidence suggests that subcutaneous UFH bid and UFH tid do not differ in effect on DVT, PE, major bleeding, and mortality. Either of the two dosing regimens of UFH or LMWH appears to be a reasonable strategy for thromboprophylaxis in medical patients. A future randomized trial comparing the two doses of UFH is very unlikely, considering the very large sample size that would be required to demonstrate a significant difference, which, if it exists, is undoubtedly small.

Santangelo, P., L. Di Biase, et al. (2010). "**Meta-analysis: age and effectiveness of prophylactic implantable cardioverter-defibrillators.**" Ann Intern Med **153**(9): 592-599.

Type of Question: Therapy **Intermediate Meta-analysis.**

Teaching Notes: Nice example of a systematic review in examining subgroup efficacy. Good clear assessment of evidence quality, forest plots, discussion points on heterogeneity. Moderate difficulty.

Abstract: BACKGROUND: Implantable cardioverter-defibrillators (ICDs) for the primary prevention of sudden cardiac death have been proven effective in several clinical trials. PURPOSE: To summarize evidence about the effectiveness of ICDs versus standard medical therapy for the primary prevention of sudden cardiac death in different age groups of patients with severe left ventricular dysfunction. DATA SOURCES: MEDLINE, Embase, CENTRAL, BioMed Central, Cardiosource, ClinicalTrials.gov, and ISI Web of Science (January 1970 to April 2010) were searched with no language restrictions. STUDY SELECTION: Two independent reviewers screened titles and abstracts to identify randomized, controlled trials of prophylactic ICD versus medical therapy in patients with severe left ventricular dysfunction that provided data about mortality outcomes for different age groups. DATA EXTRACTION: Two independent reviewers assessed risk for bias of trials and extracted patient and study characteristics and hazard ratios (HRs) relevant to all-cause mortality. DATA SYNTHESIS: Five trials (MADIT-II, DEFINITE, DINAMIT, SCD-HeFT, and IRIS) that enrolled 5783 patients (44% were elderly) were included. The primary analysis, which excluded the 2 trials enrolling patients early after acute myocardial infarction (DINAMIT and IRIS), found that prophylactic ICD therapy reduced mortality in younger patients (HR, 0.65 [95% CI, 0.50 to 0.83]; $P < 0.001$). A smaller survival benefit was found in elderly patients (HR, 0.75 [95% CI, 0.61 to 0.91]) that was not confirmed when MADIT-II patients older than 70 years were excluded or when data from DINAMIT and IRIS were included [corrected]. LIMITATIONS: Four potentially eligible trials were not included in the meta-analysis because mortality data by age group were not available. Adjustment for differences in comorbid conditions and medical therapies among patients enrolled in the trials was not possible. CONCLUSION: Available data suggest that prophylactic ICD therapy may be less beneficial for elderly patients with severe left ventricular dysfunction than for younger patients [corrected]. PRIMARY FUNDING SOURCE: None.

Hahn, D. L. (2011). "**Azithromycin for prevention of exacerbations of COPD.**" N Engl J Med **365**(23): 2236-2236; author reply 2236-2237.

Type of Question: Therapy **Beginner RCT.**

Teaching Notes: a good article to demonstrate basics of assessing validity of a therapeutic trial. Easy.

Abstract: no abstract

Huss, A., P. Scott, et al. (2009). "**Efficacy of pneumococcal vaccination in adults: a meta-analysis.**" CMAJ **180**(1): 48-58.

Type of Question: Therapy **Beginner Meta-analysis.**

Teaching Notes: article is suited to describe the methodology, advantages and limitations of a meta-analysis. Also useful for the purposes of recognizing the impact of primary trial heterogeneity on the results of a meta-analysis.

Abstract: BACKGROUND: Clinical trials and meta-analyses have produced conflicting results of the efficacy of unconjugated pneumococcal polysaccharide vaccine in adults. We sought to evaluate the vaccine's efficacy on clinical outcomes as well as the methodologic quality of the trials. METHODS: We searched several databases and all bibliographies of reviews and meta-analyses for clinical trials that compared pneumococcal polysaccharide vaccine with a control. We examined rates of pneumonia and death, taking the methodologic quality of the trials into consideration. RESULTS: We included 22 trials involving 101 507 participants: 11 trials reported on presumptive pneumococcal pneumonia, 19 on all-cause pneumonia and 12 on all-cause mortality. The current 23-valent vaccine was used in 8 trials. The relative risk (RR) was 0.64 (95% confidence interval [CI] 0.43-0.96) for presumptive pneumococcal pneumonia and 0.73 (95% CI 0.56-0.94) for all-cause pneumonia. There was significant heterogeneity between the trials reporting on presumptive pneumonia ($I^2 = 74\%$, $p < 0.001$) and between those reporting on all-cause pneumonia ($I^2 = 90\%$, $p < 0.001$). The RR for all-cause mortality was 0.97 (95%

CI 0.87-1.09), with moderate heterogeneity between trials ($I^2 = 44\%$, $p = 0.053$). Trial quality, especially regarding double blinding, explained a substantial proportion of the heterogeneity in the trials reporting on presumptive pneumonia and all-cause pneumonia. There was little evidence of vaccine protection in trials of higher methodologic quality (RR 1.20, 95% CI 0.75-1.92, for presumptive pneumonia; and 1.19, 95% CI 0.95-1.49, for all-cause pneumonia in double-blind trials; p for heterogeneity > 0.05). The results for all-cause mortality in double-blind trials were similar to those in all trials combined. There was little evidence of vaccine protection among elderly patients or adults with chronic illness in analyses of all trials (RR 1.04, 95% CI 0.78-1.38, for presumptive pneumococcal pneumonia; 0.89, 95% CI 0.69-1.14, for all-cause pneumonia; and 1.00, 95% CI 0.87-1.14, for all-cause mortality). INTERPRETATION: Pneumococcal vaccination does not appear to be effective in preventing pneumonia, even in populations for whom the vaccine is currently recommended.