

Teaching papers – Systematic Review or Meta-analysis

Juni, P., L. Nartey, et al. (2004). "Risk of cardiovascular events and rofecoxib: cumulative meta-analysis." *Lancet* 364(9450): 2021-2029.

Type of Question: Therapy (Harm) **Intermediate Meta-analysis.**

Teaching Notes: Topical question of broad clinical interest which learners find interesting. Robust cumulative meta-analysis showing the chronology of relevant RCTs on the topic demonstrating harm of this commonly prescribed medication.

Abstract: BACKGROUND: The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004. METHODS: We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint. FINDINGS: We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20742 patients) the relative risk from randomised controlled trials was 2.30 (95% CI 1.22-4.33, $p=0.010$), and 1 year later (64 events, 21432 patients) it was 2.24 (1.24-4.02, $p=0.007$). There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen; $p=0.41$) or trial duration ($p=0.82$). In observational studies, the cardioprotective effect of naproxen was small (combined estimate 0.86 [95% CI 0.75-0.99]) and could not have explained the findings of the VIGOR trial. INTERPRETATION: Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

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 ($> \text{or } =400 \text{ IU/d}$) 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.

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.

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 ≥ 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.

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.

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.**

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.

de Ferranti, S. D., J. P. Ioannidis, et al. (1998). "Are amoxycillin 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.**

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 amoxycillin 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; amoxycillin 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 amoxycillin (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: Amoxycillin 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.

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.**

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.

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.**

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.

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.**

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.

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.

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.

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.

Devereaux, P. J., W. S. Beattie, et al. (2005). "How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials." *Bmj* 331(7512): 313-321.

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

Teaching Notes: Extremely rigorous methods clearly reported make this a great teaching paper. In addition, results are counter to current practice of broadly applying b-blockers in the perioperative period to patient undergoing non-cardiac surgery. Results are good for teaching about heterogeneity. The section in the results section on exploring heterogeneity can be very instructive.

Abstract: OBJECTIVE: To determine the effect of perioperative beta blocker treatment in patients having non-cardiac surgery. DESIGN: Systematic review and meta-analysis. DATA SOURCES: Seven search strategies, including searching two bibliographic databases and hand searching seven medical journals. STUDY SELECTION AND OUTCOMES: We included randomised controlled trials that evaluated beta blocker treatment in patients having non-cardiac surgery. Perioperative outcomes within 30 days of surgery included total mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal cardiac arrest, non-fatal stroke, congestive heart failure, hypotension needing treatment, bradycardia needing treatment, and bronchospasm. RESULTS: Twenty two trials that randomised a total of 2437 patients met the eligibility criteria. Perioperative beta blockers did not show any statistically significant beneficial effects on any of the individual outcomes and the only nominally statistically significant beneficial relative risk was 0.44 (95% confidence interval 0.20 to 0.97, 99% confidence interval 0.16 to 1.24) for the composite outcome of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal cardiac arrest. Methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis showed that the evidence failed, by a considerable degree, to meet standards for forgoing additional studies. The individual safety outcomes in patients treated with perioperative beta blockers showed a relative risk for bradycardia needing treatment of 2.27 (95% CI 1.53 to 3.36, 99% CI 1.36 to 3.80) and a nominally statistically significant relative risk for hypotension needing treatment of 1.27 (95% CI 1.04 to 1.56, 99% CI 0.97 to 1.66). CONCLUSION: The evidence that perioperative beta blockers reduce major cardiovascular events is encouraging but too unreliable to allow definitive conclusions to be drawn.

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.

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 Meta-analysis.**

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.

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 $I^2 \geq 50\%$) 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.

Bischoff-Ferrari, H. A., B. Dawson-Hughes, et al. (2009). "Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials." *BMJ* 339: b3692.

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

Teaching Notes: Nicely reported meta-analysis that can be used to illustrate issues of heterogeneity. When all studies were included in the combined outcome, the results showed significant heterogeneity. However, if the data are separated into high dose and low dose, the heterogeneity is significantly improved. There is an ACP Journal club summary for this article.

Abstract: OBJECTIVE: To test the efficacy of supplemental vitamin D and active forms of vitamin D with or without calcium in preventing falls among older individuals. DATA SOURCES: We searched Medline, the Cochrane central register of controlled trials, BIOSIS, and Embase up to August 2008 for relevant articles. Further studies were identified by consulting clinical experts, bibliographies, and abstracts. We contacted authors for additional data when necessary. Review methods Only double blind randomised controlled trials of older individuals (mean age 65 years or older) receiving a defined oral dose of supplemental vitamin D (vitamin D(3) (cholecalciferol) or vitamin D(2) (ergocalciferol)) or an active form of vitamin D (1alpha-hydroxyvitamin D(3) (1alpha-hydroxycalciferol) or 1,25-dihydroxyvitamin D(3) (1,25-dihydroxycholecalciferol)) and with sufficiently specified fall assessment were considered for inclusion. RESULTS: Eight randomised controlled trials ($n=2426$) of supplemental vitamin D met our

inclusion criteria. Heterogeneity among trials was observed for dose of vitamin D (700-1000 IU/day v 200-600 IU/day; $P=0.02$) and achieved 25-hydroxyvitamin D(3) concentration (25(OH)D concentration: <60 nmol/l v ≥ 60 nmol/l; $P=0.005$). High dose supplemental vitamin D reduced fall risk by 19% (pooled relative risk (RR) 0.81, 95% CI 0.71 to 0.92; $n=1921$ from seven trials), whereas achieved serum 25(OH)D concentrations of 60 nmol/l or more resulted in a 23% fall reduction (pooled RR 0.77, 95% CI 0.65 to 0.90). Falls were not notably reduced by low dose supplemental vitamin D (pooled RR 1.10, 95% CI 0.89 to 1.35; $n=505$ from two trials) or by achieved serum 25-hydroxyvitamin D concentrations of less than 60 nmol/l (pooled RR 1.35, 95% CI 0.98 to 1.84). Two randomised controlled trials ($n=624$) of active forms of vitamin D met our inclusion criteria. Active forms of vitamin D reduced fall risk by 22% (pooled RR 0.78, 95% CI 0.64 to 0.94). **CONCLUSIONS:** Supplemental vitamin D in a dose of 700-1000 IU a day reduced the risk of falling among older individuals by 19% and to a similar degree as active forms of vitamin D. Doses of supplemental vitamin D of less than 700 IU or serum 25-hydroxyvitamin D concentrations of less than 60 nmol/l may not reduce the risk of falling among older individuals.

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.

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.

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.

Turpie, A. G., K. A. Bauer, et al. (2002). "**Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies.**" *Arch Intern Med* **162**(16): 1833-1840.

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

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

Abstract: **BACKGROUND:** Orthopedic surgery remains a condition at high risk of venous thromboembolism (VTE). Fondaparinux, the first of a new class of synthetic selective factor Xa inhibitors, may further reduce this risk compared with currently available thromboprophylactic treatments. **METHODS:** A meta-analysis of 4 multicenter, randomized, double-blind trials in patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture (N = 7344) was performed to determine whether a subcutaneous 2.5-mg, once-daily regimen of fondaparinux sodium starting 6 hours after surgery was more effective and as safe as approved enoxaparin regimens in preventing VTE. The primary efficacy outcome was VTE up to day 11, defined as deep vein thrombosis detected by mandatory bilateral venography or documented symptomatic deep vein thrombosis or pulmonary embolism. The primary safety outcome was major bleeding. **RESULTS:** Fondaparinux significantly reduced the incidence of VTE by day 11 (182 [6.8%] of 2682 patients) compared with enoxaparin (371 [13.7%] of 2703 patients), with a common odds reduction of 55.2% (95% confidence interval, 45.8% to 63.1%; P<.001); this beneficial effect was consistent across all types of surgery and all subgroups. Although major bleeding occurred more frequently in the fondaparinux-treated group (P

=.008), the incidence of clinically relevant bleeding (leading to death or reoperation or occurring in a critical organ) did not differ between groups. **CONCLUSION:** In patients undergoing orthopedic surgery, 2.5 mg of fondaparinux sodium once daily, starting 6 hours postoperatively, showed a major benefit over enoxaparin, achieving an overall risk reduction of VTE greater than 50% without increasing the risk of clinically relevant bleeding.

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.

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.

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.

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 become 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.

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.

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.

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.

Moses-Kolko, E. L., D. Bogen, et al. (2005). "**Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications.**" *Jama* 293(19): 2372-2383.

Type of Question: Harm **Moderate or Advanced Systematic Review.**

Teaching Notes: Good article if you want to expose learners to systematic review addressing harm instead of therapy

Abstract: **CONTEXT:** A neonatal behavioral syndrome linked to in utero serotonin reuptake inhibitor (SRI) exposure during the last trimester of pregnancy has been identified. The US Food and Drug Administration (FDA) and drug manufacturers have recently agreed to a class labeling change for SRIs, which include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), to include information about potential adverse events in neonates exposed in utero. Integration of data about the neonatal behavioral syndrome into the management of pregnancy in women who take SRIs is a current challenge for physicians. **OBJECTIVES:** To review evidence regarding the SRI-related neonatal syndrome and to help clinicians guide their patients in a risk-benefit decision-making process. **DATA SOURCES:** We searched MEDLINE (1966-February 2005) and PsycINFO (1974-February 2005). All articles related to neonatal signs after in utero SRI exposure were acquired, as well as unpublished data on this topic from the FDA advisory committee meeting of June 2004. References cited in case reports and studies were reviewed. Foreign-language literature was included and translated to English. **STUDY SELECTION AND DATA EXTRACTION:** Studies were included if they had clearly identified maternal SRI exposure for a minimum of the final trimester of pregnancy through delivery and assessed neonatal outcomes. We identified 13 case reports describing a total of 18 cases. Nine cohort studies met criteria. When not included in the published article, relative risks and 95% confidence intervals (CIs) were computed from raw data and summary risk ratios and 95% CIs were determined with Mantel-Haenszel estimates. **DATA SYNTHESIS:** Compared with early gestational SRI exposure or no exposure, late SRI exposure carries an overall risk ratio of 3.0 (95% CI, 2.0-4.4) for a neonatal behavioral syndrome. The most SRI-related neonatal case reports involved fluoxetine and paroxetine exposures. Neonates primarily display central nervous system, motor, respiratory, and gastrointestinal signs that are usually mild and disappear by 2 weeks of age. Medical management has consisted primarily of supportive care in special care nurseries. A severe syndrome that consists of seizures, dehydration, excessive weight loss, hyperpyrexia, or intubation is rare in term infants (1/313 quantifiable cases). There have been no reported neonatal deaths attributable to neonatal SRI exposure. **CONCLUSIONS:** Available evidence indicates that in utero exposure to SRIs during the last trimester through delivery may result in a self-limited neonatal behavioral syndrome that can be managed with supportive care. The risks and benefits of discontinuing an SRI during pregnancy need to be carefully weighed for each individual patient. Development and validation of assessment methods and clinical management strategies are critical to advancing this research.

Call, S. A., M. A. Vollenweider, et al. (2005). "**Does this patient have influenza?**" *Jama* 293(8): 987-997.

Type of Question: Diagnosis **Intermediate / Advanced Meta-analysis.**

Teaching Notes: This meta-analysis is part of the Rational Clinical Exam Series, which reports information on the diagnostic test characteristics of history and physical exam items as well as a limited number of associated diagnostic tests. This article on influenza is timely in that the distribution of flu vaccine was altered by the failure of one European manufacturer to provide expected doses of vaccine to

the United States. Thus, this paper was published in a setting of heightened public awareness of risk of influenza. Good discussion points: As with all Rational Clinical Exam articles, this is an evidence summary of diagnostic tests- thus one can discuss both systematic review methodology AND diagnosis, specifically Likelihood ratio. Excellent paragraph under statistical methods (Page 990) that defines likelihood ratio as well as diagnostic odds ratio. Stumbling block may be the large number of items listed in Tables 2 and 3 (p 992 and 993), however a clear difference in data can be noted in patients older than 60 years compared to all comers.

Abstract: CONTEXT: Influenza vaccination lowers, but does not eliminate, the risk of influenza. Making a reliable, rapid clinical diagnosis is essential to appropriate patient management that may be especially important during shortages of antiviral agents caused by high demand. OBJECTIVES: To systematically review the precision and accuracy of symptoms and signs of influenza. A secondary objective was to review the operating characteristics of rapid diagnostic tests for influenza (results available in <30 min). DATA SOURCES: Structured search strategy using MEDLINE (January 1966-September 2004) and subsequent searches of bibliographies of retrieved articles to identify articles describing primary studies dealing with the diagnosis of influenza based on clinical signs and symptoms. The MEDLINE search used the Medical Subject Headings EXP influenza or EXP influenza A virus or EXP influenza A virus human or EXP influenza B virus and the Medical Subject Headings or terms EXP sensitivity and specificity or EXP medical history taking or EXP physical examination or EXP reproducibility of results or EXP observer variation or symptoms.mp or clinical signs.mp or sensitivity.mp or specificity.mp. STUDY SELECTION: Of 915 identified articles on clinical assessment of influenza-related illness, 17 contained data on the operating characteristics of symptoms and signs using an independent criterion standard. Of these, 11 were eliminated based on 4 inclusion criteria and availability of nonduplicative primary data. DATA EXTRACTION: Two authors independently reviewed and abstracted data for estimating the likelihood ratios (LRs) of clinical diagnostic findings. Differences were resolved by discussion and consensus. DATA SYNTHESIS: No symptom or sign had a summary LR greater than 2 in studies that enrolled patients without regard to age. For decreasing the likelihood of influenza, the absence of fever (LR, 0.40; 95% confidence interval [CI], 0.25-0.66), cough (LR, 0.42; 95% CI, 0.31-0.57), or nasal congestion (LR, 0.49; 95% CI, 0.42-0.59) were the only findings that had summary LRs less than 0.5. In studies limited to patients aged 60 years or older, the combination of fever, cough, and acute onset (LR, 5.4; 95% CI, 3.8-7.7), fever and cough (LR, 5.0; 95% CI, 3.5-6.9), fever alone (LR, 3.8; 95% CI, 2.8-5.0), malaise (LR, 2.6; 95% CI, 2.2-3.1), and chills (LR, 2.6; 95% CI, 2.0-3.2) increased the likelihood of influenza to the greatest degree. The presence of sneezing among older patients made influenza less likely (LR, 0.47; 95% CI, 0.24-0.92). CONCLUSIONS: Clinical findings identify patients with influenza-like illness but are not particularly useful for confirming or excluding the diagnosis of influenza. Clinicians should use timely epidemiologic data to ascertain if influenza is circulating in their communities, then either treat patients with influenza-like illness empirically or obtain a rapid influenza test to assist with management decisions.

Rothman, R., T. Owens, et al. (2003). "Does this child have acute otitis media?" *Jama* 290(12): 1633-1640.

Type of Question: Diagnosis **Intermediate / Advanced Meta-analysis.**

Teaching Notes: Another meta-analysis is part of the Rational Clinical Exam Series. This article on otitis media in children is relevant to anyone who has ever had (or ever will have) a cranky child with a fever...Good discussion points: As with all Rational Clinical Exam articles, this is an evidence summary of diagnostic tests- thus one can discuss both systematic review methodology AND diagnosis, specifically Likelihood ratio. Excellent paragraph under statistical methods (Page 990) that defines likelihood ratio as well as diagnostic odds ratio. Stumbling block may be the large number of items listed in Tables 2 and 3 (p 992 and 993), however a clear difference in data can be noted in patients older than 60 years compared to all comers.

Abstract: CONTEXT: Acute otitis media (AOM) is one of the most common problems in pediatrics. An accurate diagnosis of AOM can guide proper treatment and follow-up. OBJECTIVE: To systematically review the literature regarding precision and accuracy of history taking and physical examination in diagnosing AOM in children. DATA SOURCES: We searched MEDLINE for English-language articles published from 1966 through May 2002. Bibliographies of retrieved articles and textbooks were also searched. STUDY SELECTION: We located studies with original data on the

precision or accuracy of history or physical examination for AOM in children. Of 397 references initially identified, 6 met inclusion criteria for analysis. DATA EXTRACTION: Two authors independently reviewed and abstracted data to calculate likelihood ratios (LRs) for symptoms and signs. DATA SYNTHESIS: Four studies of symptoms used clinical diagnosis as the criterion standard and were limited by incorporation bias. Ear pain is the most useful symptom (positive LR, 3.0-7.3); fever, upper respiratory tract symptoms, and irritability are less useful. One study of clinical signs used tympanocentesis as the criterion standard, and we adjusted the results to correct for verification bias. A cloudy (adjusted LR, 34; 95% confidence interval [CI], 28-42), bulging (adjusted LR, 51; 95% CI, 36-73), or distinctly immobile (adjusted LR, 31; 95% CI, 26-37) tympanic membrane on pneumatic otoscopy are the most useful signs for detecting AOM. A distinctly red tympanic membrane is also helpful (adjusted LR, 8.4; 95% CI, 6.7-11) whereas a normal color makes AOM much less likely (adjusted LR, 0.2; 95% CI, 0.19-0.21). CONCLUSIONS: Although many of the studies included in this analysis are limited by bias, a cloudy, bulging, or clearly immobile tympanic membrane is most helpful for detecting AOM. The degree of erythema may also be useful since a normal color makes otitis media unlikely whereas a distinctly red tympanic membrane increases the likelihood significantly.

Rathbun, S. W., G. E. Raskob, et al. (2000). "**Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review.**" *Ann Intern Med* **132**(3): 227-232.

Type of Question: Diagnosis **Intermediate / Advanced Systematic Review.**

Teaching Notes: Important paper that brought together the evidence regarding helical CT. Good discussion points: Good for discussion of how papers are graded in a systematic review. Note: this paper predates the other diagnostic paper about helical CT in the diagnosis section. Interesting to consider whether the two papers come to similar conclusions. See also Perrier A. *Annals of Internal Med* 2001;125(2):88-97 for example of an original study

Abstract: PURPOSE: To determine the sensitivity and specificity of helical computed tomography (CT) for the diagnosis of pulmonary embolism and to determine the safety of withholding anticoagulant therapy in patients who have clinically suspected pulmonary embolism and negative results on helical CT. DATA SOURCES: The MEDLINE database was searched for all reports published from 1986 to October 1999 that evaluated the use of helical CT for the diagnosis of pulmonary embolism. Bibliographies of the retrieved articles were cross-checked to identify additional studies. STUDY SELECTION: All prospective English-language studies were selected. Retrospective studies, review articles, and case reports were excluded, and 5 of the 20 identified articles were excluded. The scientific validity of the remaining 15 articles was assessed. DATA EXTRACTION: Two of the authors used a priori, pre-defined criteria to independently assess each study. A third author resolved disagreements by adjudication. The pre-defined criteria were inclusion of a consecutive series of all patients with suspected pulmonary embolism, inclusion of patients with and those without pulmonary embolism, a broad spectrum of patient characteristics, performance of helical CT and pulmonary angiography (or an appropriate reference test) in all patients, and independent interpretation of the CT scan and pulmonary angiogram (or reference test). Specific data on sensitivity and specificity and the associated 95% CIs were recorded when available. DATA SYNTHESIS: No study met all of the predefined criteria for adequately evaluating sensitivity and specificity. The reported sensitivity of helical CT ranged from 53% to 100%, and specificity ranged from 81% to 100%. In no prospective study was anticoagulant therapy withheld without further testing for venous thromboembolism in consecutive patients with suspected pulmonary embolism. One prospective study reported the outcome of selected patients with negative results on helical CT who did not receive anticoagulant therapy. CONCLUSIONS: Use of helical CT in the diagnosis of pulmonary embolism has not been adequately evaluated. The safety of withholding anticoagulant treatment in patients with negative results on helical CT is uncertain. Definitive large, prospective studies should be done to evaluate the sensitivity, specificity, and safety of helical CT for diagnosis of suspected pulmonary embolism.

McGee, S. R. and E. J. Boyko (1998). "**Physical examination and chronic lower-extremity ischemia: a critical review.**" *Arch Intern Med* **158**(12): 1357-1364.

Type of Question: Diagnosis **Beginner / Intermediate Systematic Review.**

Teaching Notes: Solid methods with comparison to reference standards. Although this is not a meta-analysis (i.e. they didn't combine results) it is a good systematic review; Good discussion points; Good paper for discussion of diagnosis, kappa (interobserver agreement) and likelihood ratios as well as systematic review. Down side: because it is not a meta-analysis, you can't discuss certain issues such as heterogeneity

Abstract: OBJECTIVE: To determine the clinical utility of physical examination in patients with suspected chronic ischemia of the lower extremities. DATA SOURCES: MEDLINE search (January 1966 to January 1997), personal files, and bibliographies of textbooks on physical diagnosis, surgery, and vascular surgery. STUDY SELECTION: Both authors independently graded the studies as level 1, 2, or 3, according to predetermined criteria. Criteria deemed essential for analysis of sensitivity, specificity, and likelihood ratios were (1) clear definition of study population, (2) clear definition of physical examination maneuver, and (3) use of an acceptable criterion standard test for comparison. RESULTS: The following positive findings help clinicians diagnose the presence of peripheral arterial disease: abnormal pedal pulses, a unilaterally cool extremity, a prolonged venous filling time, and a femoral bruit. Other physical signs help determine the extent and distribution of vascular disease, including an abnormal femoral pulse, lower-extremity bruits, warm knees, and the Buerger test. The capillary refill test and the findings of foot discoloration, atrophic skin, and hairless extremities are unhelpful in diagnostic decisions. Mathematical formulas, derived from 2 studies using multivariate analysis, allow clinicians to estimate the probability of peripheral arterial disease in their patients. CONCLUSION: Certain aspects of the physical examination help clinicians make accurate judgments about the presence of peripheral arterial disease and its distribution.

Tuon, F. F., M. N. Litvoc, et al. (2006). "**Adenosine deaminase and tuberculous pericarditis--a systematic review with meta-analysis.**" *Acta Trop* 99(1): 67-74.

Type of Question: Diagnosis **Advanced Meta-analysis.**

Teaching Notes: Good to teach likelihood ratios

Abstract: BACKGROUNDS: Adenosine deaminase (ADA) activity in pericardial fluid is a valuable aid in the diagnosis of tuberculous pericarditis (TP), but there is no systematic review performed to evaluate the benefits of ADA activity as an adjunctive test for TP diagnosis. The objective of this systematic review was to evaluate the utility of ADA activity as a diagnostic marker of TP on patients presenting with pericardial effusion. METHODS: MEDLINE, LILACS and Cochrane Library databases (1980-2005) searches to identify articles related to adenosine deaminase activity on TP diagnosis. Articles with patients with at least one TP diagnostic criteria were included. The controls were patients with other pericardial diseases with moderate or large pericardial effusion. To calculate the sensitivity, specificity, as well as positive and negative likelihood ratios we extracted the total number of confirmed TP cases over all patients with pericardial effusion as well as the number of cases with ADA activity values of 40 U/L and over. RESULTS: Thirty one studies met our initial inclusion criteria and five articles were selected. The heterogeneity limited the specificity analysis ($p=0.004$). The method yielded a sensitivity and specificity of 88% and 83%, respectively. The SROC curve presented an area with a tendency towards 1 (value of 0.9539) and corroborates the diagnostic value of ADA activity. CONCLUSIONS: The present study confirms the clinical value of ADA activity as adjunctive diagnostic marker of TP among other causes of pericardial effusion.

Hlibczuk, V., J. A. Dattaro, et al. (2010). "**Diagnostic accuracy of noncontrast computed tomography for appendicitis in adults: a systematic review.**" *Ann Emerg Med* 55(1): 51-59 e51.

Type of Question: Diagnosis **Systematic Review.**

Teaching Notes: Non-contrast appi. While most people think of SRs as involving therapy issues, there are also diagnostic SRs which offer some unique challenges from a critical appraisal perspective. This article can also serve as great substrate for a GRADE exercise or a Knowledge Translation effort.

Abstract: STUDY OBJECTIVE: We seek to determine the diagnostic test characteristics of noncontrast computed tomography (CT) for appendicitis in the adult emergency department (ED) population. METHODS: We conducted a search of MEDLINE, EMBASE, the Cochrane Library, and the bibliographies of previous systematic reviews. Included studies assessed the diagnostic accuracy of

noncontrast CT for acute appendicitis in adults by using the final diagnosis at surgery or follow-up at a minimum of 2 weeks as the reference standard. Studies were included only if the CT was completed using a multislice helical scanner. Two authors independently conducted the relevance screen of titles and abstracts, selected studies for the final inclusion, extracted data, and assessed study quality. Consensus was reached by conference, and any disagreements were adjudicated by a third reviewer. Unenhanced CT test performance was assessed with summary receiver operating characteristic curve analysis, with independently pooled sensitivity and specificity values across studies. RESULTS: The search yielded 1,258 publications; 7 studies met the inclusion criteria and provided a sample of 1,060 patients. The included studies were of high methodological quality with respect to appropriate patient spectrum and reference standard. Our pooled estimates for sensitivity and specificity were 92.7% (95% confidence interval 89.5% to 95.0%) and 96.1% (95% confidence interval 94.2% to 97.5%), respectively; the positive likelihood ratio=24 and the negative likelihood ratio=0.08. CONCLUSION: We found the diagnostic accuracy of noncontrast CT for the diagnosis of acute appendicitis in the adult population to be adequate for clinical decisionmaking in the ED setting.

Colli, A., M. Fraquelli, et al. (2006). "Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review." Am J Gastroenterol 101(3): 513-523.

Type of Question: Diagnosis **Advanced Systematic Review.**

Teaching Notes: Diagnostic tests for hepatocellular carcinoma; Lots of data – you can do calculation of LR from this paper but it will require very much set up first. However, it is a good paper for comparing likelihood ratios, discussing positive and negative LR's; Also can discuss the different cut-offs used for continuous data; Has an accompanying ACP-JC which could easily be used to simplify an exercise on this topic.

Abstract: BACKGROUND AND AIM: In patients with chronic liver disease, the accuracy of ultrasound scan (US), spiral computed tomography (CT), magnetic resonance imaging (MRI), and alpha-fetoprotein (AFP) in diagnosing hepatocellular carcinoma (HCC) has never been systematically assessed, and present systematic review was aimed at this issue. METHODS: Pertinent cross-sectional studies having as a reference standard pathological examinations of the explanted liver or resected segment(s), biopsies of focal lesion(s), and/or a period of follow-up, were identified using MEDLINE, EMBASE, Cochrane Library, and CancerLit. Pooled sensitivity, specificity, and likelihood ratios (LR) were calculated using the random effect model. Summary receiver operating characteristic (SROC) curve and predefined subgroup analyses were made when indicated. RESULTS: The pooled estimates of the 14 US studies were 60% (95% CI 44-76) for sensitivity, 97% (95% CI 95-98) for specificity, 18 (95% CI 8-37) for LR+, and 0.5 (95% CI 0.4-0.6) for LR-; for the 10 CT studies sensitivity was 68% (95% CI 55-80), specificity 93% (95% CI 89-96), LR+ 6 (95% CI 3-12), and LR- 0.4 (95% CI 0.3-0.6); for the nine MRI studies sensitivity was 81% (95% CI 70-91), specificity 85% (95% CI 77-93), LR+ 3.9 (95% CI 2-7), and LR- 0.3 (95% CI 0.2-0.5). The sensitivity and specificity of AFP varied widely, and this could not be entirely attributed to the threshold effect of the different cutoff levels used. CONCLUSIONS: US is highly specific but insufficiently sensitive to detect HCC in many cirrhotics or to support an effective surveillance program. The operative characteristics of CT are comparable, whereas MRI is more sensitive. High-quality prospective studies are needed to define the actual diagnostic role of AFP.