

Is CABG Better Than PCI for Triple-Vessel Disease?

Percutaneous Coronary Intervention Versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease.

Serruys PW, Morice M-C, et al:

N Engl J Med 2009; 360 (March 5): 961-972

In patients with previously untreated 3-vessel or left main coronary artery disease, coronary artery bypass grafting decreases the need for recurrent revascularization, but percutaneous coronary intervention decreases the incidence of stroke.

Objective: To compare percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for treatment of coronary artery disease (CAD) in patients with previously untreated 3-vessel or left main CAD (or both).

Design: Prospective randomized trial at 85 sites.

Methods/Participants: Patients were eligible if they had 3-vessel disease or left main CAD. Patients in whom it was determined that revascularization could be achieved by either CABG or PCI were randomized to 1 of the 2 treatments. Patients underwent treatment of all vessels that had a stenosis of $\geq 50\%$. The primary end point was a composite of major adverse cardiac and cerebrovascular events. These included death from any cause, stroke, infarction, or need for repeat revascularization. All patients were followed up for 12 months. The study was conducted between March 2005 and April 2007. A total of 3075 patients were included in the study and were almost equally divided between CABG and PCI.

Results: The post-procedure individual component of the primary outcome stroke and myocardial infarction (MI) was similar in the 2 groups. The incidence of major adverse events in the CABG group was 12.4% versus 17.8% in the PCI group. When evaluating secondary outcomes, repeat revascularization was significantly more common in the PCI group than in the CABG group, at 13.5% versus 5.9%. However, the rate of stroke was significantly higher in the CABG group than in the PCI group. At 12 months, the 2 groups had similar rates of death from any cause or from MI. The rate of death from cardiac causes, however, was greater in the PCI group than in the CABG group, at 3.7% versus 2.1%.

Conclusions: CABG is the standard of care for patients with 3-vessel disease or left main CAD since it had the lower rate of combined end point of major cardiac or cerebrovascular events at 1 year.

Reviewer's Comments: The bulk of this benefit of CABG was in the reduced need for revascularization; however, this was offset in large part by the increased risk of stroke in the group. I think the study really shows that each of these interventions has risks and benefits. An individual decision is, therefore, necessary for us to determine which risks the patient is willing to take. If the risk for stroke is very scary to a patient, then PCI might be the way to go, even though need for revascularization sometime in the future, or even MI, might be associated with a significantly higher risk. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Treatment

Print Tag: Refer to original journal article

Metabolic Syndrome Associated With Pulmonary Function Test Abnormalities

Lung Function Impairment and Metabolic Syndrome: The Critical Role of Abdominal Obesity.

Leone N, Courbon D:

Am J Respir Crit Care Med 2009; 179 (March 15): 509-516

Pulmonary lung function impairment is linked predominantly to abdominal obesity.

Objective: To determine the relationship of pulmonary function to the metabolic syndrome.

Design/Methods: The information was obtained from a population database of all patients in France who had undergone a physical examination and preventive medicine evaluation. Standardized questionnaires were used to obtain the clinical history, which included typical questions relating to the respiratory system. Standard definitions were used for diabetes. A waist circumference was measured on all patients, and a body mass index was calculated using the standard formula. The metabolic syndrome is defined according to the American Heart Association statement. Conditions for metabolic syndrome included 3 of the 5 following criteria: large waist circumference, elevated triglycerides, low high-density lipoprotein (HDL), high fasting glucose, and elevated blood pressure.

Results: The prevalence of the metabolic syndrome was greater in men than in women (17% vs 11%). Individual components demonstrated women to have an increased level of abdominal obesity and low HDL, whereas men had higher levels of triglycerides, blood pressure, and diabetes. Each individual component, as well as the metabolic syndrome in total, was associated with lung impairment on pulmonary function tests. After adjusting for age, sex, smoking status, and multiple other factors, lung function impairment had an adjusted odds ratio 1.28 for patients with the metabolic syndrome. Pulmonary lung function impairment was linked predominantly to abdominal obesity. Smoking status did not modify the effect between abdominal obesity and lung function impairment. The typical pattern seen on pulmonary function tests included both obstructive and restrictive lung defects. There was a significant correlation, however, between the restrictive ventilatory pattern and presence of abdominal obesity.

Conclusions: There is an independent relationship between the metabolic syndrome and lung function predominately due to abdominal obesity.

Reviewer's Comments: I am not surprised that we would tend to see more pulmonary function test abnormalities in patients who are obese than in those who are normal. What is interesting, however, is the combination of lung and cardiovascular impairment associated with the metabolic syndrome. The key take-home message here is to be on the lookout for patients who appear to have metabolic syndrome for presence of significant lung impairment since lung impairment has been associated with reduced longevity. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Metabolic Syndrome

Print Tag: Refer to original journal article

Helium Helps COPD in Rehab

Helium-Hyperoxia: A Novel Intervention to Improve the Benefits of Pulmonary Rehabilitation for Patients With COPD.

Eves ND, Sandmeyer LC, et al:

Chest 2009; 135 (March): 609-618

Breathing hyperoxia-helium mixtures during rehabilitation increases the intensity and duration of exercise, resulting in greater overall improvement in constant load exercise in patients with chronic obstructive pulmonary disease.

Objective: To determine if helium and hyperoxia can improve pulmonary rehabilitation.

Design/Participants: Prospective, 2-arm, randomized controlled trial of patients with stable chronic obstructive pulmonary disease (COPD).

Methods: Prior to onset of rehabilitation, patients underwent pulmonary function tests and exercise tests. After completion, patients underwent randomization receiving either 60% helium plus 40% oxygen or room air. Incremental exercise tests were performed in all patients, with encouragement from the therapist. Rehabilitation sessions consisted of 90 minutes of exercise and 60 minutes of education classes 3 days a week for 6 weeks. Initially, patients exercised at 50% of peak workload, which was then increased by 5% per session. A modified Borg scale was used to identify the level of dyspnea. The primary outcome was change in constant load exercise from baseline to post-rehabilitation.

Results: 19 patients were randomized for the study in each group. Receiving the hyperoxia-helium mixture increased oxygen consumption at peak by 16%; this was accompanied by an increase in peak work rate of about 12 W. Interestingly, the rate of dyspnea and leg discomfort at symptom limitation was not different in the group receiving helium-hyperoxia. Most commonly, the symptom responsible for discontinuing the exercise was leg discomfort. The change in constant load exercise was significantly greater in the helium group than in the room air group. All 4 components of the St George respiratory questionnaire were improved in the helium-hyperoxia group following rehabilitation. Patients had the most improvement in exercise tolerance if they had the most increase in the volume of exercise, as defined by frequency x duration x intensity. This was achieved in patients who received helium-hyperoxia.

Conclusions: Breathing hyperoxia-helium mixtures during rehabilitation increases the intensity and duration of exercise, resulting in greater overall improvement in constant load exercise in patients with COPD.

Reviewer's Comments: In order for muscles to improve, they need to be worked. If a patient cannot do the work not because the muscles are weak, but because of inability to ventilate and oxygenate during exercise, then pulmonary rehabilitation will not result in maximal benefit. These authors have found a unique way of allowing patients with significant obstructive lung disease to exercise for greater durations and with greater intensity by reducing the likelihood of hyperinflation and hypoxia during the exercise. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Rehabilitation

Print Tag: Refer to original journal article

Depressed COPD Patients Have Increased Mortality

Depressive Symptoms as Predictors of Mortality in Patients With COPD.

de Voogd JN, Wempe JB, et al:

Chest 2009; 135 (March): 619-625

This study provides evidence that all-cause mortality in patients with chronic obstructive pulmonary disease is strongly associated with symptoms of depression.

Objective: To investigate the association of symptoms of depression as a function of all-cause mortality in stable patients with chronic obstructive pulmonary disease (COPD).

Participants: 121 consecutive patients with COPD as evidenced by presence of airflow obstruction who were considered to be clinically stable. Patients were excluded from study if they were unable to perform lung function tests or to fill out a psychological questionnaire. Patients with malignancy and severe heart failure were also excluded.

Methods: Presence of depression was identified using the original Beck Depression Inventory. This is a self-administered test that uses 21 items to identify attitudes and symptoms of depression. For this study, a score on this questionnaire of ≥ 19 was used to define the separation between high and low depressive symptoms. In addition, patients underwent some exercise testing and pulmonary function measurements. Mortality was identified using vital statistics obtained from municipal registrations. The group comprised 78 men and 43 women. Average age of patients was 62 years, with an average FEV₁ of 37% predicted. Of patients, 20% were identified as depressed using the scoring system identified above.

Results: By the end of the study, there was a mortality rate of 63%. On univariate analysis, male gender, age, decreased peak workload, and high depression symptoms were related to mortality. When studied in a multivariate analysis, there was a significant association between mortality and presence of depression symptoms. This relationship was independent of gender, age, and decreased work ability. High depressive symptoms doubled the risk for mortality in patients with COPD.

Conclusions: This study provides evidence that all-cause mortality in patients with COPD is strongly associated with symptoms of depression.

Reviewer's Comments: In order to fully appreciate this paper, we need to look at the Kaplan-Meier survival curves to compare patients with and without symptoms of depression. The effect of depression is quite dramatic. In any event, this certainly would suggest that treatment of COPD patients should include an evaluation of their depression status and, if appropriate, patients should receive adequate therapy for this comorbidity. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Depression

Print Tag: Refer to original journal article

Increasing Ambient Temperature Spells Trouble for Patients With Respiratory Problems

High Temperature and Hospitalizations for Cardiovascular and Respiratory Causes in 12 European Cities.

Michelozzi P, Accetta G, et al:

Am J Respir Crit Care Med 2009; 179 (March 1): 383-389

In this study, for a 1°C increase in temperature above threshold, respiratory admissions increased by an average of 4.5%.

Objective: To determine the effect of temperature on respiratory admissions to the hospital.

Design/Methods: The study analyzed data from 12 cities including Dublin, Milan, Paris, Rome, and Zurich, among others. Each city was responsible for providing hospital admission and meteorological data as well as air pollution indices for 3 years within the period of 1990 to 2001. The maximum apparent temperature was used as the exposure index, which includes a relationship between the actual air temperature and the dewpoint temperature, basically creating a thermal discomfort index. The analysis was restricted to the warm months of the calendar year from April through September. Confounding influences such as day of the week, calendar month, and trends in temperatures were included in the analysis. Nitric oxide and Sulfur dioxide levels were available as well as ozone exposure. Two models were used for temperature exposure that occurred immediately with the temperature change and those with a lag time from 0 to 3 days after exposure to the high temperature.

Results: Throughout the 12 cities, there was a considerable variation in the average apparent temperature from a low of 14.7°C in Dublin to a high of 29.5°C in Valencia. There was also a very heterogeneous relationship between the temperature and admission rate across the cities. Interestingly, there was no association between most cities and temperature for cardiovascular and cerebrovascular admissions. In fact, there was a negative relationship found in some Mediterranean cities; however, for respiratory illnesses, there was a definite increase in hospital admissions with increasing temperature observed throughout most of the cities; this was also age specific. For a 1°C increase in temperature above threshold, respiratory admissions increased by an average of 4.5%.

Conclusions: High temperatures appear to have a significant impact on respiratory admissions, particularly in the elderly population. There does not appear to be a significant cardiovascular morbidity effect. However, the authors do note that previous data have shown a cardiovascular mortality rate associated with temperature increases.

Reviewer's Comments: I think this is a rather interesting study and points out something that most of us are fairly familiar with. There is a significant relationship between respiratory morbidity and temperature. The authors do not provide any sort of explanation as to why this is the case. It is possible that there is greater exposure to pollutants during periods of high temperature, but this was not evident in this study. The other interesting thing is that, in cardiovascular disease, there appears to be a significant impact on mortality but no increased rate of cardiovascular admissions. This too remains to be explained. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: High Temperatures

Print Tag: Refer to original journal article

ECG Useful in Prognosis of Patients With PE

Prognostic Value of ECG Among Patients With Acute Pulmonary Embolism and Normal Blood Pressure.

Vanni S, Polidori G, et al:

Am J Med 2009; 122 (March): 257-264

Right ventricular strain is associated with adverse outcome, and when added to echocardiographic evidence of right ventricular dysfunction, is a good prognostic indicator, even in patients with normal blood pressure.

Objective: To determine the utility of ECG in patients with pulmonary embolism (PE) but normal blood pressure.

Participants/Methods: 557 patients were objectively confirmed to have a PE. Thirty-six patients were excluded because they had shock on admission and an additional 123 patients were excluded because they had either a previous episode of PE or significant lung disease. Fourteen additional patients were excluded because they could not undergo an echocardiogram because of poor body habitus. The result was 386 patients that made up the cohort for the study. The average age was 67 years, 60% were female, and 34% had idiopathic pulmonary embolism. CT was used to confirm the diagnosis in 195 patients, and perfusion scanning confirmed diagnosis in 162. Overall, 3% of patients required vena cava filter because of a contraindication to anticoagulation and 11% were treated with thrombolytic agents. Six percent met the combined end point of death or clinical deterioration with an absolute mortality rate of 3%, and 52% of patients had right ventricular dysfunction as evidenced by echocardiographic signs. There was a significant correlation between ventricular dysfunction and deterioration or death or increased hospital stay. These patients also tended to have a lower blood pressure than those patients with a normal ECG. Twelve percent of patients with right ventricular strain on ECG reached the composite end point and 6% died. A univariate analysis demonstrated that the presence of right ventricular strain was associated with death or clinical deterioration, with an odds ratio of 3.75. Even during the multivariate analysis, right ventricular strain still demonstrated an association with the composite end point or death. In total, 51% of patients who had right ventricular dysfunction on echo demonstrated right ventricular strain on ECG as well. Patients were then characterized into 4 groups based on whether they had normal or abnormal echocardiograms and ECGs. Patients who had right ventricular strain and right ventricular dysfunction had a significantly increased risk of death or clinical deterioration compared to any other combination.

Conclusions: Right ventricular strain is associated with adverse outcome, and when added to echocardiographic evidence of right ventricular dysfunction prognosticates fairly well, even in patients with normal blood pressure.

Reviewer's Comments: Once again, this study demonstrates that ECG does have some benefit in identifying patients who are at risk of pulmonary embolism. In this study, both the clinical outcome and duration of hospitalization were associated with ECG changes. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Blood Pressure

Print Tag: Refer to original journal article

NIV Masks Leak, Can Affect Ventilation

Intentional Leaks in Industrial Masks Have a Significant Impact on Efficacy of Bilevel Noninvasive Ventilation: A Bench Test Study.

Borel JC, Sabil A, et al:

Chest 2009; 135 (March): 669-677

This study found that intentional leak affected trigger delay only when lung compliance and resistance were normal; however, intentional leak did significantly reduce pressure time product in both restrictive as well as normal lung conditions.

Objective: To identify the effect of an intentional leaking mask on noninvasive ventilation (NIV) efficacy.

Methods: 7 different masks were the focus of this study. The masks were connected to a mannequin head and then standard ventilator tubing was used to connect to the ventilator. Then the mannequin was connected to a test lung through 22-mm diameter tubing that was approximately 60 cm long. The test lung allowed for changes in compliance and resistance as well as respiratory rate, inspiratory time, and tidal volume. Each mask was tested at different settings by changing the compliance and the resistance. All testing was done at 15 cycles per minute with inspiratory duration of about 1 second. In addition, 4 different bilevel ventilators were tested. They were all programmed to deliver an inspiratory pressure of 14 cm and an expiratory pressure of 4 cm. The measurements for efficacy included the trigger delay, defined as the time interval between onset of inspiratory effort and onset of detectable pressurization, and the trigger pressure time product, which reflects the sensitivity of the ventilator as well as its ability to deliver high flow rates.

Results: Ventilators varied widely on their trigger delay and on their pressure time product. Intentional leak affected trigger delay only when lung compliance and resistance were normal. However, intentional leak did significantly reduce pressure time product in both restrictive and normal lung conditions. Inspiratory assistance was significantly related to the levels of intentional leak in obstructive lung conditions, but not in normal and restrictive lung conditions. In addition, intentional leaks had an effect on tidal volume delivered in obstructive patients and in normal conditions, but not during restrictive lung testing.

Conclusions: Intentional leaks in the mask can impair efficacy of the ventilator at various kinds of lung conditions--some being affected during restrictive lung conditions and others during obstructive lung conditions.

Reviewer's Comments: It appears from the study that the use of NIV is not as simple as one would think. Leaking is a significant problem, whether intentional or unintentional. Various ventilators perform better than others, but unfortunately, it appears that there is no perfect choice. In addition, there does not appear to be a perfect mask available either, but some do perform better than others. I would refer you to the article if you think you need more specific information about which ventilator mask combination might be best for your patients. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Intentional Leaking Mask

Print Tag: Refer to original journal article

PCR Useful in Diagnosis of Pneumocystis Pneumonia

Polymerase Chain Reaction for Diagnosing Pneumocystis Pneumonia in Non-HIV Immunocompromised Patients With Pulmonary Infiltrates.

Azoulay E, Bergeron A, et al:

Chest 2009; 135 (March): 655-661

In immunocompromised patients who do not have AIDS but do have acute pulmonary infiltrates, polymerase chain reaction correlates fairly well with clinical evidence of a pneumocystis infection.

Background: Pneumocystis is responsible for pneumonia in many immunocompromised subjects. Typically, we associate this with HIV-infected patients with CD4 counts of <200. However, it can also occur in other patients with immunodeficiency. Because of its difficulty being cultured, it is often hard to study and to know, for certain, if the patient is infected with this organism.

Objective: To evaluate the feasibility of polymerase chain reaction (PCR) in this cohort of patients.

Methods: Patients were included if they were immunocompromised but did not have AIDS. Patients were required to have bilateral pulmonary infiltrates and/or respiratory failure. The decision to perform a bronchoalveolar lavage or to induce sputum was at the sole discretion of the clinician. PCR results were not used for the diagnosis of pneumocystis pneumonia. Attending physicians were actually blinded to the results. Standard techniques were used for staining and identifying pneumocystis from the sputum and for performing the PCR. A total of 448 patients were studied, all of whom were immunocompromised but did not have AIDS. Alveolar lavage was obtained in 351 patients and induced sputum in 97.

Results: Standard staining was positive in 8.7% of the specimens, yielding a definitive diagnosis of pneumocystis. PCR was positive in 34 of these 39 patients. Of the 409 patients who had negative stains for pneumocystis, 32 had a positive PCR. Follow-up studies were performed on patients with false-positive PCR. Fourteen of these patients had either probable or definite pneumocystis; the remaining 7 patients were characterized as being colonized.

Conclusions: In immunocompromised patients who do not have AIDS but who do have acute pulmonary infiltrates, PCR correlates fairly well with clinical evidence of a pneumocystis infection. The authors suggest that a negative PCR allows withdrawing of treatment for pneumocystis.

Reviewer's Comments: Overall, this new PCR evaluation has a sensitivity of approximately 87%, a specificity of about 92%, a negative predictive value of almost 99%, and a positive predictive value of about 52%. What will be important to determine with this test, as it invariably will be used in a more diverse cohort of patients, will be whether positive- and negative-predictive values still hold up? Or will we now start seeing greater false-positive and greater false-negative results? At the current time, based on these data, this technique should be an adjunct to standard staining of induced sputum or bronchoalveolar lavage fluid but not a replacement. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Pneumocystis

Print Tag: Refer to original journal article

Treating Depression in COPD Patients Does Not Change Mortality

Effect of Depression Care and Outcomes in COPD Patients With Depression.

Jordan N, Lee TA, et al:

Chest 2009; 135 (March): 626-632

In patients with chronic obstructive pulmonary disease and depression, interaction with health care providers is important to their well-being by following guideline care for depression, but this does not significantly affect hospitalization or mortality rates.

Objective: To determine if the effective treatment for depression in patients with chronic obstructive pulmonary disease (COPD) improves respiratory outcomes.

Participants: The study was performed on veterans with a history of COPD and a diagnosis of depression. The diagnoses were obtained by looking at ICD-9 codes. None of the patients in the study could have been receiving treatment for depression at the time. They were, however, allowed into the study if they had received the proper treatment at least 90 days prior to enrollment.

Methods: For each patient, the investigators identified mortality rate and hospitalizations over a 2-year period of follow-up. The final cohort consisted of almost 5500 patients after appropriate exclusions were applied. During the acute phase of the depression, about 10% of the patients received therapy consistent with guidelines for the treatment of depression. Patients who received the treatment in a mental health setting were more likely to receive appropriate treatment than those seeking treatment only from a primary care provider. The 2-year COPD hospitalization rate was 6.6% and was unrelated to receiving or not receiving appropriate care for depression. There was no statistically significant difference, but there was a trend in a lower 2-year mortality rate in patients who received appropriate depression care. No relationship was found between the use of appropriate therapy for depression and mortality rate. Predictors of mortality were older age, higher acuity of illness requiring multiple visits to health care providers, and prior hospitalization.

Conclusions: In patients with COPD and depression, interaction with health care providers is important to their well-being by following guideline care for depression, but this does not significantly affect hospitalization or mortality rates.

Reviewer's Comments: The first study (review #4 on this program) looked at the effect of depression on outcomes in patients with COPD and demonstrated a relationship between depression and poor outcome in this cohort of patients. The study, unfortunately, suggests that if patients are identified as having depression and are given depression treatment according to standard guidelines, it has no effect on hospitalization or mortality rate, at least over a 2-year period. Perhaps longer follow-up would have resulted in a delineation of benefit, or perhaps, as discussed in a previous article on this subject, depression is not causing mortality in COPD but the COPD is causing patients to become severely depressed. In any event, appropriate therapy within the regimen of depression medications in patients who are depressed is beneficial for the quality of life regardless of the effect on lung disease. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Depression

Print Tag: Refer to original journal article

Incentives Help Smokers Quit

A Randomized Controlled Trial of Financial Incentives for Smoking Cessation.

Volpp KG, Troxel AB, et al:

N Engl J Med 2009; 360 (February 12): 699-709

Financial incentives for smoking cessation can significantly increase positive results.

Objective: To determine if financial incentives improve outcomes of smoking cessation.

Participants/Methods: Participants were recruited between 2005 and 2006. They were identified using a questionnaire that included history of their cigarette use and other tobacco products. Subjects were eligible if they were aged >18 years and were current smokers. All participants were followed up for at least 12 months. Biochemical verification of cigarette cessation was performed. Participants in the incentive group were notified that they would receive \$100 financial reward for completion of the study; if smoking cessation was confirmed at 6 months, they would receive an additional \$250; if they continued for an additional 6 months without smoking, they would receive another \$400. Patients who reported that they had stopped smoking were asked to provide a saliva or urine sample for confirmation. Randomization proceeded according to work sites, income, and cigarette consumption. The primary end point was self-reporting of abstinence; 436 participants were in the incentive group and 442 were in the control group. All baseline data were similar between groups at onset of the study.

Results: The 9- and 12-month rate of cessation of cigarette smoking as measured chemically was 14.7% in the incentive group and 5% in the control group. The rate of participation in the smoking program was greater in the incentive group than in the control group (15% vs 5%). Members who participated in the smoking cessation program had significantly higher rates of cessation than did members of the control group who participated. The chemically identified smoking cessation rate 6 months after study enrollment was 20.9% in the incentive group and 11.8% in the control group. Interestingly, at 15 and 18 months, the rates dropped off in both groups (9.4% vs 3.6%); the odds ratio for being smoke-free in the incentive group was 3.28. Members of the incentive group across all stratification models demonstrated significantly greater rates of smoking cessation than did members of the control group.

Conclusions: In the study of employees at a large firm, financial incentives for smoking cessation significantly increased positive results.

Reviewer's Comments: I guess it now becomes a question of who is going to pay. In this study, it was beneficial to the corporation to reduce the number of employees who smoked since this could improve productivity. Perhaps health maintenance organizations and the government will see a benefit in helping cigarette smokers quit. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Smoking Cessation

Print Tag: Refer to original journal article

Macrolides for All Cases of CAP?

Impact of Macrolide Therapy on Mortality for Patients With Severe Sepsis Due to Pneumonia.

Restrepo MI, Mortensen EM, et al:

Eur Respir J 2009; 33 (January): 153-159

Macrolides have immunomodulatory effects that may be beneficial in treating patients with severe sepsis secondary to community-acquired pneumonia.

Background: Macrolides have immunomodulatory effects. They have been demonstrated, to modulate the effects of tumor necrosis factor alpha1, interleukin (IL)-1, IL-6, and IL-9.

Objective: To evaluate the effect of macrolide therapy on 30- and 90-day mortality in patients with severe sepsis caused by community-acquired pneumonia (CAP).

Design: Retrospective cohort study.

Participants: Patients hospitalized with CAP at 2 academic teaching tertiary care hospitals in San Antonio, Texas. Of 787 patients hospitalized between January 1, 1999, and December 31, 2002, the authors identified 237 who met criteria for severe sepsis.

Methods: These 237 patients were divided into 2 groups: those who received macrolide therapy within 48 hours of admission and those who did not. The 2 groups were similar in most characteristics. At the time of presentation, the macrolide-treated group was more likely to be hypoxic and hyponatremic. Non-macrolide patients were more likely to have cerebral vascular disease (23% vs 8%) and chronic renal disease (26% vs 13%). The 2 groups were similar in the severity of illness scores, rates of ICU admission, need for mechanical ventilation, and need for vasopressor support.

Results: 30- and 90-day mortality rates were lower for patients who received macrolide antibiotics than for those who did not. The 30-day mortality rate for patients who received macrolide antibiotics was 11% versus 29% for those who did not; the 90-day mortality rate was 12% for patients who received macrolide antibiotics compared to 34% for those who did not.

Conclusions: The immunomodulatory effects of macrolides may be important when they are used to treat patients with CAP and severe sepsis.

Reviewer's Comments: There are obvious limitations to this study. It was retrospective and was not randomized. The authors suggest that the immunomodulatory effects of macrolide antibiotics may be as important as or even more important than their antimicrobial effects. Clearly, prospective randomized trials are needed to confirm these postulations. Perhaps trials could be conducted to evaluate the effects of macrolide administration in patients with severe sepsis from non-respiratory conditions. (Reviewer-Richard A. Nusser, MD).

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Keywords: Macrolide Therapy

Print Tag: Refer to original journal article

Thrombolysis for Acute PE? Use Cautiously

Thrombolytic Therapy and Mortality in Patients With Acute Pulmonary Embolism.

Ibrahim SA, Stone RA, et al:

Arch Intern Med 2008; 168 (November 10): 2183-2190

In a large database, thrombolysis for pulmonary embolism (PE) was associated with an increased risk of death compared with not being thrombolysed after controlling for confounders. Hospitalists should use thrombolysis in PE with caution.

Background: The most common indication for thrombolysis in pulmonary embolism (PE) is cardiopulmonary compromise. Yet, there has been increasing interest in use of thrombolysis in patients who are hemodynamically stable but may have other indications. Very little is known about clinical outcomes associated with thrombolytics in PE in real-world settings.

Objective: To determine the prevalence of thrombolytic therapy for acute PE and to evaluate 30-day and in-hospital mortality associated with its use.

Design: Retrospective review of a large database.

Methods: Using a large Pennsylvania database (186 acute-care hospitals), the authors analyzed all patients discharged with a diagnosis of PE from 2000 to 2002. They compared 30-day and in-hospital mortality for those who received thrombolysis and those who did not. Because thrombolysis was not randomly allocated, the authors had to try to control for clinical features that would make someone more likely to receive thrombolytics. They created a propensity score that allowed them to compare treatment effects for patients with similar predicted probabilities of receiving thrombolytic therapy (let them compare 2 patients who were clinically similar but 1 received thrombolysis and the other did not).

Results: Only 2.4% of all 15,116 patients discharged with a diagnosis of PE were given thrombolytics. Without adjustment, overall 30-day mortality rates were 17.4% in patients who were thrombolysed compared to 8.6% in those who were not. After propensity score adjustment, odds ratio for 30-day mortality depended on the likelihood of receiving thrombolysis. For those patients who were least likely to receive thrombolytics (but did anyway), odds ratios for 30-day mortality ranged from 2.0 to 3.9. In no group of patients, even those clinically most likely to receive thrombolysis (ie, hypotensive), was there a decreased mortality associated with lytic therapy.

Conclusions: In this large database, thrombolysis was infrequently used. However, for patients who were unlikely candidates for thrombolysis based on their clinical features but who were given lytics anyway, these patients had a higher risk of mortality. The authors argue that use of thrombolysis in acute PE in cases other than hemodynamic instability may incur an increased risk of death.

Reviewer's Comments: A complicated study from a statistical standpoint as the study doesn't really tell us if there is an increased or decreased risk of death with use of thrombolytics in acute PE. However, it tells us that, in patients who may not have clear clinical indications for thrombolysis, there may be an increased risk of death if they are treated. This article adds more literature arguing against use of thrombolysis in PE except in settings of hemodynamic instability. We should probably all use lysis in PE with caution. (Reviewer-Bradley A. Sharpe, MD).

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Keywords: Acute Pulmonary Embolism

Print Tag: Refer to original journal article

CXR Progression in CAP Predicts Higher Mortality

Radiologic Progression of Pulmonary Infiltrates Predicts a Worse Prognosis in Severe Community-Acquired Pneumonia Than Bacteremia.

Lisboa T, Blot S, et al:

Chest 2009; 135 (January): 165-172

In patients with severe community-acquired pneumonia (in the ICU), chest radiograph progression of infiltrates at 48 hours predicts a higher risk of shock and ICU mortality and is more predictive than bacteremia.

Background: Mortality among patients with severe community-acquired pneumonia (CAP; those admitted to the ICU) remains high. Patients with severe CAP often are bacteremic or have progression of their infiltrates on chest radiograph (CXR), but the prognostic significance of these findings is not known.

Objective: To examine the prognostic significance of CXR progression and bacteremia in patients with severe CAP.

Design: Prospective cohort study.

Participants/Methods: In 33 Spanish hospitals, consecutive patients admitted to the ICU with severe CAP were enrolled. All patients had blood cultures done before antibiotics and a repeat CXR at 48 hours. Radiographic/CXR progression was defined as a >50% increase in the size of opacities. Patients were stratified into 4 groups: (1) those with both CXR progression and bacteremia, (2) those with CXR progression alone, (3) those with bacteremia alone, and (4) those with neither. Multivariate analysis was performed, controlling for all possible confounding factors.

Results: A total of 457 patients with severe CAP were enrolled. In adjusted analyses, patients with both CXR progression and bacteremia and those with CXR progression alone were at increased risk of shock and increased risk of ICU death when compared to patients with neither (odds ratios range, 3.1 to 8.9). Patients with bacteremia alone were not at increased risk of shock or at increased risk of ICU death when compared to patients with neither CXR progression nor bacteremia. These results persisted when groups were broken down by pneumococcal versus non-pneumococcal bacteremia.

Conclusions: In this large prospective study of patients with severe CAP, CXR progression at 48 hours increased the risk of death by >3 times when compared to patients without progression or bacteremia. CXR progression was a better predictor of shock or ICU death than was bacteremia, which, interestingly, was not associated with worse outcomes. Future studies should focus on etiologies of CXR progression as well as targeted therapies.

Reviewer's Comments: A well-done and straightforward prospective study revealing that, in severe CAP, if the CXR significantly worsens at 48 hours, it is predictive of an increased risk for death in the ICU. Curiously, bacteremia in severe CAP did not predict an increased risk of shock or death in the ICU. It is likely that bacteremia actually is a risk factor for death, but it doesn't add any additional risk above other reasons that patients develop severe CAP. It is not clear how this study should change practice as it was merely observational. Future studies may help us with focused therapies in patients with worsening chest radiographs. In the meantime, just be aware that CXR progression is a bad sign in patients with severe CAP. (Reviewer-Bradley A. Sharpe, MD).

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Keywords: Severe Community-Acquired Pneumonia

Print Tag: Refer to original journal article

Follow Up Primary Pulmonary Coccidioidomycosis Patients for Prolonged Periods

Factors and Outcomes Associated With the Decision to Treat Primary Pulmonary Coccidioidomycosis.

Ampel NM, Giblin A, et al:

Clin Infect Dis 2009; 48 (January 15): 172-178

Provision of prolonged therapy in patients with primary pulmonary coccidioidomycosis does not prevent subsequent extrapulmonary dissemination.

Background: Although the incidence of symptomatic coccidioidomycosis is increasing, the optimal management of primary pulmonary coccidioidomycosis has never been carefully examined. In the past, clinicians were hesitant to treat this syndrome because of the toxicity of amphotericin B.

Objective: To determine the outcome of a cohort of patients who were prospectively followed after diagnosis of primary pulmonary coccidioidomycosis at the Southern Arizona Veterans Affairs Health Care System.

Design: Observational study.

Participants/Methods: Ultimately, 105 patients were diagnosed with primary pulmonary coccidioidomycosis; 54 were treated and 51 were not. Treatment usually consisted of fluconazole 400 mg daily for variable lengths of time.

Results: Sex, age, ethnicity, serological titer, and underlying disease were not significant predictors of those patients who were given therapy, but symptom score (≥ 2) and presence of a positive *Coccidioides* culture were. A total clinical score (≥ 5), which was a composite of the symptom score and culture result, was also predictive of receiving therapy. Only 43 patients were followed prospectively in the clinic, but in all of these patients, both the clinical score and titer of the coccidioidal serological test decreased significantly. The median decline in clinical scores was similar regardless of whether or not the patient received therapy. Two patients who were initially treated with antifungal therapy and later stopped developed disseminated coccidioidomycosis. It was possible to perform a retrospective analysis on all but 4 of these 105 patients through review of electronic medical records. The 50 patients who were never prescribed antifungal therapy did not develop evidence of worsening or relapsed coccidioidomycosis. On the other hand, of 50 patients who initially were treated with antifungal therapy, 5 developed relapse of pulmonary disease and 3 developed more widespread disease.

Reviewer's Comments: Compared to previous studies, the 3% rate of extrathoracic dissemination in these patients with primary pulmonary coccidioidomycosis is high. However, even if patients with significant disease received prolonged courses of azole therapy, it did not prevent subsequent extrapulmonary dissemination. Consequently, it is probably not warranted to provide antifungal therapy just to prevent dissemination in patients with primary pulmonary coccidioidomycosis. Any patient with primary pulmonary coccidioidomycosis should be followed for prolonged periods; rising *Coccidioides* complement fixation titers are useful in this regard. (Reviewer-Richard J. Hamill, MD).

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Keywords: Primary Pulmonary Coccidioidomycosis

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PPV Predicts Fluid Responsiveness Despite Lung Protective Ventilation

Prediction of Fluid Responsiveness in Acute Respiratory Distress Syndrome Patients Ventilated With Low Tidal Volume and High Positive End-Expiratory Pressure.

Huang CC, Fu JY, et al:

Crit Care Med 2008; 36 (October): 2810-2816

In early acute respiratory distress syndrome patients ventilated with low tidal volumes and high positive end-expiratory pressure, pulse pressure variation >11.8% accurately predicts responsiveness to a fluid challenge.

Background: In critically ill patients, predicting response to fluid administration is crucial to avoid undesired hypovolemia or fluid overload. Static pre-load parameters, such as the central venous pressure (CVP) and the pulmonary arterial occlusion pressure, cannot accurately discriminate between responders and non-responders to a fluid challenge.

Objective: To evaluate the accuracy of pulse pressure variation (PPV) and stroke volume variation (SVV) in predicting fluid responsiveness using pulse contour analysis in acute respiratory distress syndrome (ARDS).

Design: Prospective observational study in an ICU of a tertiary medical center.

Participants: 22 patients ventilated with a lung-protective strategy (mean tidal volume of 6.8 mL/kg predicted body weight, and mean positive end-expiratory pressure (PEEP) of 14 cm H₂O). All had early (<3 days) ARDS and were sedated and paralyzed for the study.

Methods: CVP, pulmonary capillary wedge pressure, and cardiac index from a pulmonary artery catheter, along with intrathoracic blood volume, global end-diastolic volume, SVV, and PPV were recorded from a PiCCoPlus monitor, before and after 500 mL IV hydroxyethyl starch.

Results: After the fluid bolus index, CVP, pulmonary capillary wedge pressure, global end-diastolic volume, and intrathoracic blood volume significantly increased, and PPV and SVV significantly decreased. The PPV showed the largest area under the receiver-operating characteristic curve. A baseline PPV >11.8% predicted a response to the fluid bolus with a sensitivity of 68% and a specificity of 100%.

Conclusions: Despite small tidal volumes and reduced lung compliance, PPV can still accurately predict the cardiac output response to a fluid bolus.

Reviewer's Comments: In mechanically ventilated patients without cardiac arrhythmia or spontaneous inspiratory efforts, many studies have shown that PPV is a very specific and sensitive parameter to identify responders to fluid loading. However, there have been no previous studies on patients with ARDS on mechanical ventilation with low tidal volumes and high PEEP levels. Since both of these lung-protective maneuvers may reduce PPV at baseline, the predictive value of PPV in this population has not been clear until now. This study is consistent with the results of a previous study (de Backer et al, *Intensive Care Medicine*, 2005). Interestingly, both studies show a threshold value PPV of 11.8% for predicting fluid responsiveness. However, the mean PEEP level was higher in the present study (14 vs 11 cm H₂O). With a higher PEEP, the performance of PPV at the same threshold value of 11.8% was better. This corroborates previous findings by emphasizing that PEEP exaggerates the cyclic changes in pleural and transpulmonary pressures and offsets the disadvantageous effect of low tidal volumes in predicting fluid responsiveness. (Reviewer-Martin F. Britos, MD).

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Keywords: Fluid Responsiveness

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Cardiac CT Can Be Useful Tool for Patients Prior to AF Ablation

Utility of Nongated Multidetector Computed Tomography for Detection of Left Atrial Thrombus in Patients Undergoing Catheter Ablation of Atrial Fibrillation.

Martinez MW, Kirsch J, et al:

JACC Cardiovasc Imaging 2008; 2 (January): 69-76

In patients at low risk for thromboembolism, cardiac CT may be able to accurately exclude left atrial appendage thrombus.

Background: Patients undergoing atrial fibrillation (AF) ablation generally undergo cardiac computed tomography (CT) to assess pulmonary veins and other proximate structures. Transesophageal echocardiograms are also part of the pre-ablation workup to rule out left atrial appendage (LAA) thrombus. These imaging procedures increase total cost and are also associated with complications unique to these tests.

Objective: To assess sensitivity and specificity of cardiac CT to detect LAA thrombus.

Participants/Methods: 402 patients who underwent AF ablation at Mayo clinic where studied. All patients had non-gated cardiac CT performed according to standard protocol. All patients also had multiplanar transesophageal echocardiograms (TEE) performed within 72 hours of the CT scan.

Results: 362 of 402 patients (90%) had no thrombus seen on cardiac CT. This was confirmed by TEE. Of patients, 40 (10%) had abnormal or under-filled LAA by CT. Of these 40 patients, 9 had definite thrombus by TEE. The remaining 31 patients had at least moderate spontaneous echo contrast. Sensitivity of CT to detect thrombus was 100%, specificity was 92%, negative-predictive value (NPV) was 100%, and positive-predictive value (PPV) was 23%.

Conclusions: Among patients referred for AF ablation, a normal LAA by CT ruled out presence of LAA thrombus. Thus cardiac CT could potentially avoid the need for multiple imaging modalities prior to AF ablation.

Reviewer's Comments: The authors have shown that non-gated 64-slice CT done before AF ablation has an excellent NPV for ruling out LAA thrombus. The PPV, however, is poor. Thus if CT shows poor visualization of contrast in the LAA, these patients may need further workup in the form of a TEE. However, if the CT shows a normally opacified LAA, especially in AF patients with a low risk for thromboembolism, further TEE could be avoided. Since this study population included patients with a relatively lower risk for LAA thrombus, the results cannot be extrapolated to higher-risk populations. (Reviewer-Anoop C. Parameswaran, MD).

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Keywords: Left Atrial Thrombus

Print Tag: Refer to original journal article

Dronedarone May One Day Be an Option When Treating AF

Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation.

Hohnloser S, Crijns HJGM, et al:

N Engl J Med 2009; 360 (February): 668-678

Dronedarone may have significant anti-arrhythmic effects without the toxicity associated with amiodarone.

Background: Amiodarone is one of the mainstays in the pharmacologic treatment of atrial fibrillation (AF). Amiodarone, however, is associated with significant pulmonary, thyroid, and liver toxicity mainly due to its iodine moiety. The search is ongoing for a pharmacologic agent with the efficacy of amiodarone without the associated toxicity. Dronedarone, an amiodarone-analogue devoid of the iodine moiety is undergoing clinical trials to assess its efficacy and safety. Previous studies have suggested that dronedarone is superior to placebo in the maintenance of sinus rhythm. Concerns were raised, however, about increased mortality with use of dronedarone in at least 1 study.

Objective: To define the efficacy and safety profile of dronedarone in patients with paroxysmal or persistent AF.

Participants/Methods: 4628 patients were randomized to either dronedarone 400 mg twice daily (2301 patients) or placebo (2327 patients) and followed for an average of 21 months. Primary outcome was the composite of a first hospitalization for a cardiovascular cause or death. Secondary outcomes were death from any cause, cardiovascular death and hospitalization for a cardiovascular event. Patients were included if they had AF or atrial flutter with 1 other risk factor (including age ≥ 70 years, hypertension, diabetes, stroke, or structural heart disease). No direct comparison to amiodarone was done.

Results: Groups were well matched at baseline. Patients receiving dronedarone were significantly less likely to have a primary end point of hospitalization for cardiovascular events or death (31.9% vs 39.4%; hazard ratio [HR] 0.76; $P < 0.001$). The dronedarone group was also less likely to have cardiovascular death or a cardiovascular-related hospitalization. There was a significant reduction in arrhythmic deaths and a non-significant trend toward less overall death in the dronedarone group. Incidence of hospitalization for AF was also significantly lower in the dronedarone group. Overall, medication discontinuation rates were similar in both groups. Dronedarone recipients had higher rates of bradycardia, QT-interval prolongation, nausea, diarrhea, rash, and a rise in serum creatinine. There were no significant differences in incidence of thyroid or pulmonary toxicity.

Conclusions: This study suggests that dronedarone has efficacy in AF patients with significant reductions in the rate of overall death or hospitalization for cardiovascular events. It is also associated with a decrease in the risk of cardiovascular death and a trend toward lower overall death. The risk profile, as predicted, is different from that of amiodarone with no significant increases in thyroid and pulmonary toxicity compared to placebo.

Reviewer's Comments: Dronedarone is not currently approved in the United States. This is mainly due to concerns about its safety profile. This study may change the perception about this drug and accelerate its approval process. Until that happens, the search continues for safe and efficacious replacements for amiodarone. (Reviewer-Khalid Almuti, MD).

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Keywords: Atrial Fibrillation

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