Scanning the Literature

Internal Medicine Reviews by Steven Granier, MD
Family Medicine Reviews by Edward Martin, MD
Cardiology Reviews by Richard Milani, MD

Do Inflamed Hearts Predict Cardiovascular Disease?

Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342:836-843.

Background: Since inflammation is believed to have a role in the pathogenesis of cardiovascular events, measurement of markers of inflammation has been proposed as a method to improve the prediction of the risk of these events. **Methods**: We conducted a prospective, nested case-control study among 28,263 apparently healthy postmenopausal women over a mean follow-up period of three years to assess the risk of cardiovascular events associated with base-line levels of markers of inflammation. The markers included high-sensitivity C-reactive protein (hs-CRP), serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule type 1 (sICAM-1). We also studied homocysteine and a variety of lipid and lipoprotein measurements. Cardiovascular events were defined as death from coronary heart disease, nonfatal myocardial infarction or stroke, or the need for coronary-revascularization procedures. **Results**: Of the 12 markers measured, hs-CRP was the strongest univariate predictor of the risk of cardiovascular events; the relative risk of events for women in the highest as compared with the lowest quartile for this marker was 4.4 (95 percent confidence interval, 2.2 to 8.9). Other markers significantly associated with the risk of cardiovascular events were serum amyloid A (relative risk for the highest as compared with the lowest quartile, 3.0), sICAM-1 (2.6), interleukin-6 (2.2), homocysteine (2.0), total cholesterol (2.4), LDL cholesterol (2.4), apolipoprotein B-100 (3.4), HDL cholesterol (0.3), and the ratio of total cholesterol to HDL cholesterol (3.4). Prediction models that incorporated markers of inflammation in addition to lipids were significantly better at predicting risk than models based on lipid levels alone ($P<0.001$). The levels of hs-CRP and serum amyloid A were significant predictors of risk even in the subgroup of women with LDL cholesterol levels below 130 mg per deciliter (3.4 mmol per liter), the target for primary prevention established by the National Cholesterol Education Program. In multivariate analyses, the only plasma markers that independently predicted risk were hs-CRP (relative risk for the highest as compared with the lowest quartile, 1.5; 95 percent confidence interval, 1.1 to 2.1) and the ratio of total cholesterol to HDL cholesterol (relative risk, 1.4; 95 percent confidence interval, 1.1 to 1.9). **Conclusions**: The addition of the measurement of C-reactive protein to screening based on lipid levels may provide an improved method of identifying persons at risk for cardiovascular events.

Comments: Cardiovascular disease has a large impact on our medical practices every day. And because this is a serious problem, we constantly look for ways to predict the risk of cardiovascular events. Since inflammation is felt to play a role in the pathogenesis of cardiovascular events (death from coronary heart disease, nonfatal infarction or stroke, or need for coronary bypass), this study sought to evaluate the use of inflammatory markers as predictors of these events. A potential concern is the numerous other conditions (i.e. infections, rheumatologic conditions) that can increase CRP.

Of the markers evaluated in the study, hs-CRP predicted increased relative risk for cardiovascular events. This even included a subset of patients with goal range LDL-cholesterol levels<130. hs-CRP may help identify patients with increased risk of cardiovascular events even if more widely accepted risk factors are not present. The hs-CRP may allow more aggressive, earlier primary prevention of cardiovascular disease in certain patients.

A Clinical Trial for the Health Food Store

Khatta M, Alexander BS, Krichten CM, et al. The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med 2000; 132:636-640.

Background: Coenzyme Q10 is commonly used to treat congestive heart failure on the basis of data from several unblinded, subjective studies. Few randomized, blinded, controlled studies have evaluated objective measures of cardiac performance. **Objective**: To determine the effect of coenzyme Q10 on peak oxygen consumption, exercise duration, and ejection fraction. **Design**: Randomized, double-blind, controlled trial. **Setting**: University and Veterans Affairs hospitals. **Patients**: 55 patients who had congestive heart failure with New York Heart Association class III and IV symptoms, ejection fraction less than 40%, and peak oxygen consumption less than 17.0 mL/kg per minute (or <50% of predicted) during standard therapy were randomly assigned. Forty-six patients completed the study. **Intervention**: Coenzyme Q10, 200 mg/d, or placebo. **Measurements**: Left ventricular ejection fraction (measured by radionuclide ventri-culography) and peak oxygen consumption and exercise duration (measured by a graded exercise evaluation using the Naughton protocol) with continuous metabolic monitoring. **Results**: Although the mean (+/-SD) serum concentration of coenzyme Q10 increased from 0.95+/- 0.62 microg/mL to 2.2+/-1.2 microg/mL in patients who received active treatment, ejection fraction, peak oxygen consumption, and exercise duration remained unchanged in both the coenzyme Q10 and placebo groups. **Conclusion**: Coenzyme Q10 does not affect ejection fraction, peak oxygen consumption, or exercise duration in patients with congestive heart failure receiving standard medical therapy.

Comments: Many days in my medical practice, I am asked about various products that can be found at the local health food store or over the Internet. Several ask about "Co Q10" for improving their heart condition. As is often the case, many of these products have not been scientifically studied. This study sought to evaluate Co Q10 supplementation on LV ejection traction, and exercise tolerance.

Although it was a small study, it was a randomized, double blind, controlled study. Previous smaller uncontrolled or even anecdotal studies have shown positive (but sometimes contradictory) results. While this study showed an increase in the concentration level of the enzyme in the study subjects, no statistically significant change in ejection traction or peak oxygen consumption was identified. Larger studies with higher doses may be beneficial, but in this time of increasing interest in "natural" treatments, it is unlikely that patients will stop buying these supplements. In this case, however, it is nice to be able to provide scientific data to answer their question "Should I take this supplement?"

Does Estrogen Prevent Alzheimer's Progression?

Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA 2000; 283:1007-1015.

Context: Several reports from small clinical trials have suggested that estrogen replacement therapy may be useful for the treatment of Alzheimer disease (AD) in women. **Objective**: To determine whether estrogen replacement therapy affects global, cognitive, or functional decline in women with mild to moderate AD. **Design**: The Alzheimer's Disease Cooperative Study, a randomized, double-blind, placebo-controlled clinical trial conducted between October 1995 and January 1999. **Setting**: Thirty-two study sites in the United States. **Participants**: A total of 120 women with mild to moderate AD and a Mini-Mental State Examination score between 12 and 28 who had had a hysterectomy. **Interventions**: Participants were randomized to estrogen, 0.625 mg/d (n = 42), or 1.25 mg/d (n = 39), or to identically appearing placebo (n = 39). One subject withdrew after randomization but before receiving medication; 97 subjects completed the trial. **Main Outcome Measures**: The primary outcome measure was change on the Clinical

Global Impression of Change (CGIC) 7-point scale, analyzed by intent to treat; secondary outcome measures included other global measures as well as measures of mood, specific cognitive domains (memory, attention, and language), motor function, and activities of daily living; compared by the combined estrogen groups vs the placebo group at 2, 6, 12, and 15 months of follow-up. **Results**: The CGIC score for estrogen vs placebo was 5.1 vs 5.0 (P = .43); 80% of participants taking estrogen vs 74% of participants taking placebo worsened (P = .48). Secondary outcome measures also showed no significant differences, with the exception of the Clinical Dementia Rating Scale, which suggested worsening among patients taking estrogen (mean posttreatment change in score for estrogen, 0.5 vs 0.2 for placebo; P = .01). **Conclusions**: Estrogen replacement therapy for 1 year did not slow disease progression nor did it improve global, cognitive, or functional outcomes in women with mild to moderate AD. The study does not support the role of estrogen for the treatment of this disease. The potential role of estrogen in the prevention of AD, however, requires further research.

Comments: As the country's population ages, more patients are developing Alzheimer's disease often leading to poorer quality of life, not to mention increased medical costs. Because women with Alzheimer's live longer than men with Alzheimer's, there are twice as many women with this disorder.

Numerous studies have evaluated treatment of Alzheimer's disease, including specific evaluation for slowing the progression of its course. This 1-year study evaluated the use of estrogen replacement for improvement of global, cognitive, or functional outcome and found no statistically significant difference with estrogen versus placebo. There was a brief benefit of low dose estrogen on mental status examination but this improvement did not persist.

We will have to continue research for the treatment of Alzheimer's disease and continue to consider estrogen for primary prevention of this increasingly costly condition.

Does Caffeine Prevent Parkinson's?

Ross GW, Abbott RD, Petrovich H, et al. Association of coffee and caffeine intake with the risk of Parkinson disease.
JAMA 2000, 283:2674-2679.

Context: The projected expansion in the next several decades of the elderly population at highest risk for Parkinson's disease (PD) makes identification of factors that promote or prevent the disease an important goal. **Objective**: To explore the association of coffee and dietary caffeine intake with risk of PD. **Design, Setting, and Participants**: Data were analyzed from 30 years of follow-up of 8004 Japanese-American men (aged 45-68 years) enrolled in the prospective longitudinal Honolulu Heart Program between 1965 and 1968. **Main Outcome Measures**: Incident PD, by amount of coffee intake (measured at study enrollment and 6-year follow-up) and by total dietary caffeine intake (measured at enrollment). **Results**: During follow-up, 102 men were identified as having PD. Age-adjusted incidence of PD declined consistently with increased amounts of coffee intake, from 10.4 per 10000 person-years in men who drank no coffee to 1.9 per 10000 person-years in men who drank at least 28 oz/d ($P<.001$ for trend). Similar relationships were observed with total caffeine intake ($P<.001$ for trend) and caffeine from noncoffee sources ($P=.03$ for trend). Consumption of increasing amounts of coffee was also associated with lower risk of PD in men who were never, past, and current smokers at baseline ($P=.049$, $P=.22$, $P=.02$, respectively, for trend). Other nutrients in coffee, including niacin, were unrelated to PD incidence. The relationship between caffeine and PD was unaltered by intake of milk and sugar. **Conclusions**: Our findings indicate that higher coffee and caffeine intake is associated with a significantly lower incidence of PD. This effect appears to be independent of smoking. The data suggest that the mechanism is related to caffeine intake and not to other nutrients contained in coffee.

Comments: Parkinson's disease affects about 3% of adults over age 65. Depending on the severity, the condition can be a major burden physically, psychologically, and financially on patients and their families. This study analyzed data from 30 years of follow-up from the Honolulu Heart program and found that the incidence of Parkinson's disease was nearly 10 times greater in those who drank no caffeine compared with those who had at least 28 ounces per day.

One limitation is that the data were obtained from Japanese-American men somewhat later in life. The same association may not apply to women, younger patients, and other ethnic groups. Also, the observational nature of the study makes it not as strong as a prospective study. More evaluation will be needed to further qualify the relationship between caffeine and Parkinson's disease.

Dr. Granier is on staff in Ochsner's Department of Internal Medicine and a regular contributor to Scanning the Literature.

Serving Three Masters

Wynia MK, Cummins DS, VanGeest JB, et al. Physician manipulation of reimbursement rules for patients: between a rock and a hard place. JAMA 2000;283:1858-1865.

Context: Health plan utilization review rules are intended to enforce insurance contracts and can alter and constrain the services that physicians provide to their patients. Physicians can manipulate these rules, but how often they do so is unknown. **Objective**: To determine the frequency with which physicians manipulate reimbursement rules to obtain coverage for services they perceive as necessary, and the physician attitudes and personal and practice characteristics associated with these manipulations. **Design, Setting, and Participants**: A random national sample of 1124 practicing physicians was surveyed by mail in 1998; the response rate was 64% (n = 720). **Main Outcome Measure**: Use of 3 different tactics "sometimes" or more often in the last year: (1) exaggerating the severity of patients' conditions; (2) changing patients' billing diagnoses; and/or (3) reporting signs or symptoms that patients did not have to help the patients secure coverage for needed care. **Results**: Thirty-nine percent of physicians reported using at least 1 tactic "sometimes" or more often in the last year. In multivariate models comparing these physicians with physicians who "never" or "rarely" used any of these tactics, physicians using these tactics were more likely to (1) believe that "gaming the system" is necessary to provide high-quality care today (odds ratio [OR], 3.67; 95% confidence interval [CI], 2.54-5.29); (2) have received requests from patients to deceive insurers (OR, 2.44; 95% CI, 1.72-3.45); (3) feel pressed for time during patient visits (OR, 1.69; 95% CI, 1.21-2.37); and (4) have more than 25% of their patients covered by Medicaid (OR, 1.60; 95% CI, 1.08-2.38). Notably, greater worry about prosecution for fraud did not affect physicians' use of these tactics (P = .34). Of those reporting using these tactics, 54% reported doing so more often now than 5 years ago. **Conclusions**: A sizable minority of physicians report manipulating reimbursement rules so patients can receive care that physicians perceive is necessary. Unless novel strategies are developed to address this, greater utilization restrictions in the health care system are likely to increase physicians' use of such manipulative "covert advocacy" tactics.

Comments: It was bound to happen. From the earliest vestiges of our medical education, we were encouraged to do what was in the best interest of patients and their families. Like a horse with blinders, we sought this goal and side issues, such as reimbursement, were easily ignored. Over the last few decades, we have seen tremendous technology advancement and expansion with subsequent increase in the cost of medical care. The focus on third party payers has shifted somewhat from encouraging utilization to utilization management. The rules of the game seem to change on a daily basis. The rule makers would still say the patient is at the center of their decisions, but they would also admit to the reality of outside economic, political, and demographic influences. The angst generated by these potential conflicts has put unusual stress on all parties involved. As we try and change the gray areas back to black and white, the author of this study suggests there will be "covert advocacy." I overtly agree.

Less is More and More is Less

Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial.
JAMA 2000; 283:1583-1590.

Context: The optimal antimicrobial regimen and treatment duration for acute uncomplicated pyelonephritis are unknown. **Objective**: To compare the efficacy and safety of a 7-day ciprofloxacin regimen and a 14-day trimethoprim-sulfame-thoxazole regimen for the treatment of acute pyelonephritis in women. **Design:** Randomized, double-blind comparative trial conducted from October 1994 through January 1997. **Setting**: Twenty-five outpatient centers in the United States. Patients: Of 378 enrolled premenopausal women aged at least 18 years with clinical diagnosis of acute uncomplicated pyelonephritis, 255 were included in the analysis. Other individuals were excluded for no baseline causative organism, inadequate receipt of study drug, loss to follow-up, no appropriate cultures, and other reasons. **Interventions**: Patients were randomized to oral ciprofloxacin, 500 mg twice per day for 7 days (with or without an initial 400-mg intravenous dose) followed by placebo for 7 days (n = 128 included in analysis) vs trimethoprim-sulfamethoxazole, 160/800 mg twice per day for 14 days (with or without intravenous ceftriaxone, 1 g) (n = 127 included in the analysis). **Main Outcome Measure**: Continued bacteriologic and clinical cure, such that alternative antimicrobial drugs were not required, among evaluable patients through the 4- to 11-day posttherapy visit, compared by treatment group. **Results**: At 4 to 11 days posttherapy, bacteriologic cure rates were 99% (112 of 113) for the ciprofloxacin regimen and 89% (90 of 101) for the trimethoprim-sulfamethoxazole regimen (95% confidence interval [CI] for difference, 0.04-0.16; P = .004). Clinical cure rates were 96% (109 of 113) for the ciprofloxacin regimen and 83% (92 of 111) for the trimethoprim-sulfamethoxazole regimen (95% CI, 0.06-0.22; P = .002). Escherichia coli, which caused more than 90% of infections, was more frequently resistant to trimethoprim-sulfamethoxazole (18%) than to ciprofloxacin (0%; P<.001). Among trimethoprim-sulfamethoxazole-treated patients, drug resistance was associated with greater bacteriologic and clinical failure rates (P<.001 for both). Drug-related adverse events occurred in 24% of 191 ciprofloxacin-treated patients and in 33% of 187 trimethoprim-sulfamethoxazole-treated patients, respectively (95% CI, -0.001 to 0.2). **Conclusions**: In our study of outpatient treatment of acute uncomplicated pyelonephritis in women, a 7-day ciprofloxacin regimen was associated with greater bacteriologic and clinical cure rates than a 14-day trimethoprim-sulfamethoxazole regimen, especially in patients infected with trimethoprim-sulfamethoxazole-resistant strains.

Comments: In the quest to find the perfect treatment for an infection, we are always looking for the most effective and the least costly medication with the fewest side effects and the greatest ease of administration. This study proves once again that medication costs can be trumped by effectiveness and that longer

duration of treatment is not always better. The findings of this study continue to move us away from the practices of years gone by when all cases of pyelonephritis were admitted and treated with intravenous antibiotics until the patient was free of fever for 24 hours. The gap between evidence based practical treatment and the sometimes less substantiated traditional treatment is narrowing but there are still many questions to be posed and answered.

An Ounce is Worth a Pound

Lieu TA, Ray GT, Black SB, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children.
JAMA 2000;283:1460-1468.

Context: Pneumococcal conjugate vaccine for infants has recently been found effective against meningitis, bacteremia, pneumonia, and otitis media. **Objective**: To evaluate the projected health and economic impact of pneumococcal conjugate vaccination of healthy US infants and young children. **Design**: Cost-effectiveness analysis based on data from the Northern California Kaiser Permanente randomized trial and other published and unpublished sources. **Setting and Patients**: A hypothetical US birth cohort of 3.8 million infants. **Interventions**: Hypothetical comparisons of routine vaccination of healthy infants, requiring 4 doses of pneumococcal conjugate vaccine (at 2, 4, 6, and 12-15 months), and catch-up vaccination of children aged 2 to 4.9 years requiring 1 dose, with children receiving no intervention. **Main Outcome Measures**: Cost per life-year saved and cost per episode of meningitis, bacteremia, pneumonia, and otitis media prevented. **Results**: Vaccination of healthy infants would prevent more than 12000 cases of meningitis and bacteremia, 53000 cases of pneumonia, 1 million episodes of otitis media, and 116 deaths due to pneumococcal infection. Before accounting for vaccine costs, the vaccination program would save $342 million in medical and $415 million in work-loss and other costs from averted pneumococcal disease. Vaccination of healthy infants would result in net savings for society if the vaccine cost less than $46 per dose, and net savings for the health care payer if the vaccine cost less than $18 per dose. At the manufacturer's list price of $58 per dose, infant vaccination would cost society $80000 per life-year saved or $160 per otitis media episode prevented (other estimated costs would be $3200 per pneumonia case prevented, $15000 for bacteremia, and $280000 for meningitis). The cost-effectiveness of an additional program to administer 1 dose of vaccine to children aged 2 to 4.9 years would vary depending on the children's ages, relative risks of pneumococcal disease, and vaccine cost. **Conclusions**: Pneumococcal conjugate vaccination of healthy US infants has the potential to be cost-effective. To achieve cost savings, its cost would need to be lower than the manufacturer's list price. In addition to tangible costs, the vaccine should be appraised based on the less tangible value of preventing mortality and morbidity from pneumococcal disease.

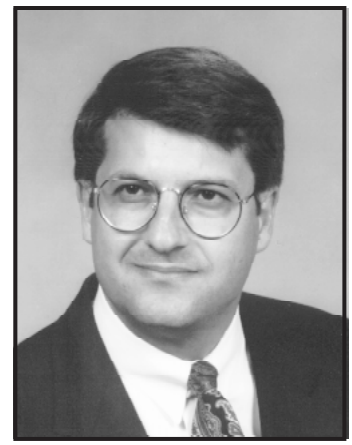
Comments: Although this study focuses on identifying the monetary savings of preventing morbidity and mortality associated with pneumococcal meningitis, sepsis, pneumonia, and otitis media using the recently approval pneumococcal conjugate vaccine in healthy US infants, the potential for preventing noneconomic maladies could be an even greater benefit. In this era of cost analysis, one must not overlook the more humanitarian goals of reducing pain and suffering for patients and their families. The need for less antibiotic use and, therefore, less bacterial resistance is another valuable derivative. With healthier children, one might also expect a greater potential for learning. The benefits could increase exponentially, proving the inflated value of an ounce of prevention.

Exploiting Technology

Johnston B, Wheeler L, Deuser J, Sousa KH. Outcomes of the Kaiser Permanente Tele-Home Health Research Project.
Arch Fam Med 2000;9:40-45.

Context: Level of acuity and number of referrals for home health care have been escalating exponentially. As referrals continue to increase, health care organizations are encouraged to find more effective methods for providing high-quality patient care with cost savings. **Objective**: To evaluate the use of remote video technology in the home health care setting as well as the quality, use, patient satisfaction, and cost savings from this technology. **Design**: Quasi-experimental study conducted from May 1996 to October 1997. **Setting**: Home health department in the Sacramento, Calif, facility of a large health maintenance organization. **Participants**: Newly referred patients diagnosed as having congestive heart failure, chronic obstructive pulmonary disease, cerebral vascular accident, cancer, diabetes, anxiety, or need for wound care were eligible for random assignment to intervention (n = 102) or control (n = 110) groups. **Intervention**: The control and intervention groups received routine home health care (home visits and telephone contact). The intervention group also had access to a remote video system that allowed nurses and patients to interact in real time. The video system included peripheral equipment for assessing cardiopulmonary status. **Main Outcome Measures**: Three quality indicators (medication compliance, knowledge of disease, and ability for self-care); extent of use of services; degree of patient satisfaction as reported on a 3-part scale; and direct and indirect costs of using the remote video technology. **Results**: No differences in the quality indicators, patient satisfaction, or use were seen. Although the average direct cost for home health services was $1830 in the intervention group and $1167 in the control group, the total mean costs of care, excluding home health care costs, were $1948 in the intervention group and $2674 in the control group. **Conclusions**: Remote video technology in the home health care setting was shown to be effective, well received by patients, capable of maintaining quality of care, and to have the potential for cost savings. Patients seemed pleased with the equipment and the ability to access a home health care provider 24 hours a day. Remote technology has the potential to effect cost savings when used to substitute some in-person visits and can also improve access to home health care staff for patients and caregivers. This technology can thus be an asset for patients and providers.

Comments: The use of remote video technology as an adjunct to home healthcare is a vision whose time has come. As society becomes more comfortable with "video interfacing," the potential for careful monitoring of a patient in their home setting by qualified medical personnel at a remote site could prove extremely valuable, especially in rural areas. Tele-Medicine Projects throughout the country have extended care to many areas where shortages of specialty physicians exist. This new twist focusing on nursing care seems to be a logical extension. Quality indicators, at least in this study, were maintained. Although this may sound a little Orwellian, its potential benefits could bring outpatient care to a new and more comprehensive level.



Dr. Martin is the Chairman of Ochsner's Family Medicine Department.

The Results Are In: Beta-Blockers Work

Hjalmarson A, Goldstein S, Fagerberg B, et al. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). JAMA 2000; 283:1295-1337.

Context: Results from recent studies on the effects of beta1-blockade in patients with heart failure demonstrated a 34% reduction in total mortality. However, the effect of beta1-blockade on the frequency of hospitalizations, symptoms, and quality of life in patients with heart failure has not been fully explored. **Objective:** To examine the effects of the beta1-blocker controlled-release/extended-release metoprolol succinate (metoprolol CR/XL) on mortality, hospitalization, symptoms, and quality of life in patients with heart failure. **Design:** Randomized, double-blind controlled trial, preceded by a 2-week single-blind placebo run-in period, conducted from February 14, 1997, to October 31, 1998, with a mean follow-up of 1 year. **Setting:** Three hundred thirteen sites in 14 countries. **Participants:** Patients (n = 3991) with chronic heart failure, New York Heart Association (NYHA) functional class II to IV, and ejection fraction of 0.40 or less who were stabilized with optimum standard therapy. **Interventions:** Patients were randomized to metoprolol CR/XL, 25 mg once per day (NYHA class II), or 12.5 mg once per day (NYHA class III or IV), titrated for 6 to 8 weeks up to a target dosage of 200 mg once per day (n = 1990); or matching placebo (n = 2001). **Main Outcome Measures:** Total mortality or any hospitalization (time to first event), number of hospitalizations for worsening heart failure, and change in NYHA class, by intervention group; quality of life was assessed in a substudy of 741 patients. **Results:** The incidence of all predefined end points was lower in the metoprolol CR/XL group than in the placebo group, including total mortality or all-cause hospitalizations (the prespecified second primary end point; 641 vs 767 events; risk reduction, 19%; 95% confidence interval [CI], 10%-27%; P<.001); total mortality or hospitalizations due to worsening heart failure (311 vs 439 events; risk reduction, 31%; 95% CI, 20%-40%; P<.001), number of hospitalizations due to worsening heart failure (317 vs 451; P<.001); and number of days in hospital due to worsening heart failure (3401 vs 5303 days; P<.001). NYHA functional class, assessed by physicians, and McMaster Overall Treatment Evaluation score, assessed by patients, both improved in the metoprolol CR/XL group compared with the placebo group (P = .003 and P = .009, respectively). **Conclusions:** In this study of patients with symptomatic heart failure, metoprolol CR/XL improved survival, reduced the need for hospitalizations due to worsening heart failure, improved NYHA functional class, and had beneficial effects on patient well-being.

Comments: The data are now overwhelming with regards to the beneficial effects of B_1-blockade in patients with chronic stable heart failure. Currently less than 30% of eligible heart failure patients are being treated with B_1-blocker therapy. B_1-blocker therapy in eligible patients has been shown to have dramatic effects on mortality, hospitalization frequency, and New York Heart Association (NYHA) functional classification, as well as patient well-being and should be adopted as routine therapy for most patients with chronic heart failure.

Prehospital Thrombosis: The Sooner the Better

Morrison LJ, Verbeek PR, McDonald AC, el al. Mortality and pre-hospital thrombolysis for acute myocardial infarction: a meta-analysis. JAMA 2000; 283:2686-2692.

Context: Early administration of thrombolysis for acute myocardial infarction (AMI) may improve survival if safely and appropriately delivered. No systematic reviews that have comprehensively examined this topic exist in the literature. **Objective:** To perform a meta-analysis of randomized controlled trials of prehospital vs in-hospital thrombolysis for AMI measuring in-hospital mortality. **Data Sources:** The Cochrane search strategy was used to search MEDLINE, EMBASE, and the Science Citation Index (1982-1999); Dissertation Abstracts (1987-1999); and Current Contents (1994-1999) for the terms thrombolysis, thrombolysis therapy, prehospital, and acute myocardial

infarction. In addition, text and journal article bibliographies were hand searched, the National Institutes of Health Web site was reviewed, and primary authors and thrombolytic drug manufacturers were contacted for unpublished studies. **Study Selection:** Randomized controlled trials of prehospital vs in-hospital thrombolysis for AMI measuring all-cause hospital mortality were included. Two authors independently reviewed 175 citations by title, abstract, or complete article. After exclusion of 30 duplicate citations, 145 studies remained, of which 6 studies and 3 follow-up studies met the inclusion criteria. **Data Extraction:** Independent data abstraction by 2 reviewers blinded to the journal, title, and author was confirmed by consensus. Trial quality was independently assessed by 2 other coauthors, blinded to the author, title, journal, introduction, and discussion. **Data Synthesis:** The results of the 6 randomized trials (n=6434) were pooled and indicated significantly decreased all-cause hospital mortality among patients treated with prehospital thrombolysis compared with in-hospital thrombolysis (odds ratio, 0.83; 95% confidence interval, 0.70-0.98). Results were similar regardless of trial quality or training and experience of the provider. Estimated (SE) time to thrombolysis was 104 (7) minutes for the prehospital group and 162 (16) minutes for the in-hospital thrombolysis group (P=.007). **Conclusions:** Our meta-analysis suggests that prehospital thrombolysis for AMI significantly decreases the time to thrombolysis and all-cause hospital mortality.

Comments: Cardiovascular disease remains the leading cause of death in North America and acute myocardial infarction accounts for a large proportion of these deaths. Although thrombolytic therapy decreases mortality, benefit depends on the time to treatment. Clinical research has focused on reducing the time to treatment with the advent of chest pain protocols, rapid triage, and thrombolysis in the emergency department. Despite these efforts, the time to thrombolysis, or "time to needle" remains high.

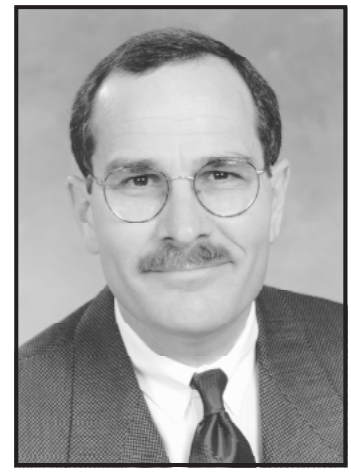
One way to address this is to administer thrombolysis before the patient arrives in the hospital. The Nation Heart Attack Alert Program concluded in 1997 that prehospital thrombolysis reduces mortality in a subgroup of patients who require long (> 1 hour) out-of-hospital transport times to an emergency department. This meta-analysis attempted to critically appraise and summarize all randomized controlled trials of prehospital versus in-hospital thrombolysis for acute myocardial infarction. The primary outcome measure was all-cause hospital mortality; secondary outcome measures were scene times, time to thrombolytic treatment, postinfarct ejection fraction, infarct size, Q-wave infarction, and adverse events, including ventricular fibrillation, cardiogenic shock, hypotension, bradycardia, bleeding, and stroke. The results of six pooled randomized trials (n=6434) indicated significantly decreased all-cause hospital mortality among patients treated with prehospital thrombolysis compared with in-hospital thrombolysis (risk reduction 17%). Results were similar regardless of trial quality or training and experience of the provider. Considering these findings, prehospital thrombolysis should be used to treat acute myocardial infarction in patients meeting standard criteria.

Pulse Pressure Is the Clearer Determinant of Risk for Older Hypertensives

Blacher J, Staessen JA, Girerd X, et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients.
Arch Intern Med 2000;160:1085-1089.

Background: Current guidelines for the management of hypertension rest almost completely on the measurement of systolic and diastolic blood pressure. However, the arterial blood pressure wave is more correctly described as consisting of a pulsatile (pulse pressure) and a steady (mean pressure) component. **Objective:** To explore the independent roles of pulse pressure and mean pressure as determinants of cardiovascular prognosis in older hypertensive patients. **Methods:** This meta-analysis, based on individual patient data, pooled the results of the European Working Party on High Blood Pressure in the Elderly trial (n = 840), the Systolic Hypertension in Europe Trial (n = 4695), and the Systolic Hypertension in China Trial (n = 2394). The relative hazard rates associated with pulse pressure and mean pressure were calculated using Cox regression analysis, with stratification for the 3 trials and with adjustments for sex, age, previous cardiovascular complications, smoking, and treatment group.

Results: A 10-mm Hg wider pulse pressure increased the risk of major cardiovascular complications; after controlling for mean pressure and the other covariates, the increase in risk ranged from approximately 13% for all coronary end points (P = .02) to nearly 20% for cardiovascular mortality (P = .001). In a similar analysis, mean pressure predicted the incidence of cardiovascular complications but only after removal of pulse pressure as an explanatory variable from the model. Furthermore, the probability of a major cardiovascular end point increased with higher systolic blood pressure; at any given level of systolic blood pressure, it also increased with lower diastolic blood pressure, suggesting that the wider pulse pressure was driving the risk of major complications. **Conclusions:** In older hypertensive patients, pulse pressure not mean pressure is the major determinant of cardiovascular risk. The implications of these findings for the management of hypertensive patients should be further investigated in randomized controlled outcome trials in which the pulsatile component of blood pressure is differently affected by antihypertensive drug treatment.



Dr. Milani is the Chairman of Ochsner's Department of Population Medicine and The Ochsner Journal's Associate Editor of Population Medicine .

Comments: Traditional teaching has suggested that systolic and diastolic pressure have equal importance in predicting risk for subsequent cardiovascular events. This approach to hypertension is underscored in guidelines that have defined cardiovascular risk by the elevation of systolic and/or diastolic blood pressure. There is now increasing evidence from several large trials, as assessed in the above meta-analysis, that pulse pressure serves as the single best predictor of subsequent cardiovascular events when compared to either systolic or diastolic blood pressure. Each of these trials reveals that at a given systolic blood pressure, the lower the diastolic blood pressure, the greater the resultant cardiovascular risk. These data have also been reproduced in the Framingham Heart Study in middle-aged and elderly patients and underscore the importance of treating patients with large pulse pressures, in particular patients with isolated systolic hypertension.