BNP May Help Guide Heart Failure Therapy

BNP-Guided vs Symptom-Guided Heart Failure Therapy: The Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) Randomized Trial.

Pfisterer M, Buser P, et al:

JAMA 2009; 301 (January 28): 383-392

BNP may help guide treatment for CHF better than symptoms in patients aged 60 to 74 years.

Background: Therapy for congestive heart failure (CHF) is often adjusted based on symptoms. It is not known whether brain natriuretic peptide (BNP) would be a better tool to guide heart failure therapy.

Objective: To compare the use of symptoms versus BNP in the adjustment of heart failure therapies over 18 months.

Design: Single-blind, randomized, controlled trial.

Participants: Patients aged ≥60 years with New York Heart Association (NYHA) class II or greater symptoms on therapy, a hospitalization within the previous year for CHF, and BNP >400 pg/mL if age was <75 years or >800 pg/mL if age was ≥75 years. Patients were recruited to 15 centers in Switzerland and Germany.

Methods: 622 patients (80% with systolic heart failure) were divided into 2 age groups: 60 to 74 years and ≥75 years. Patients were randomized to medication adjustment guided by symptoms or BNP. Medications changes were based on a guideline-driven algorithm. Goals of therapy were NYHA class II symptoms or less or BNP <2 times the upper limit of normal. Patients were evaluated at baseline and at 1, 3, 6, 12, and 18 months. The primary end points were survival free of hospitalization and quality of life at 18 months.

Results: Patients in the BNP-guided group were more likely to have their medication uptitrated than those in the symptom-guided group. Survival free of hospitalization was no different in the 2 treatment groups, but survival free of heart failure hospitalization was significantly less in the 60- to 74-year-old BNP-guided group. Quality-of-life measures improved in both groups but were not significantly different. Serious side effects were no different in the 2 treatment groups. Conclusions: Treatment guided by BNP does not reduce survival free of hospitalization or quality of life, but does reduce hospitalizations due to heart failure in patients aged 60 to 74 years with CHF.

Reviewer’s Comments: This study suggests that physicians may need to be more aggressive in uptitrating medications in patients with heart failure. BNP-guided therapy may be a useful strategy in some patients, especially those aged <75 years. (Reviewer-Deborah L. Greenberg, MD).

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Keywords: Therapy

Print Tag: Refer to original journal article
Both COX-2 selective and nonselective NSAIDs are associated with increased mortality in patients with heart failure.

**Background:** Nonsteroidal anti-inflammatory drugs (NSAIDs), including old-fashioned over-the-counter (OTC) medications, can cause sodium and fluid retention and exacerbate heart failure (HF), but are widely perceived to be safe and often used by cardiac patients.

**Objective:** To assess the risk of hospitalization and death associated with NSAID use in patients with HF.

**Design:** Retrospective cohort study.

**Participants:** 107,000 Danish patients with HF.

**Methods:** Using the Danish central registry of hospitalizations, investigators identified all those surviving an initial hospitalization for HF from 1995 to 2004. They then reviewed the national prescription registry for NSAID prescriptions. In Denmark, OTC NSAIDs are available only in very small quantities and are not covered by health insurance as prescriptions are, so virtually all NSAIDs are dispensed by prescription. The daily dose was defined as low (for example, rofecoxib ≤25 mg/day, ibuprofen ≤1200 mg/day, or naproxen ≤500 mg/day) or high dose.

**Results:** 34% of HF patients received at least 1 prescription for a selective COX-2 inhibitor or a nonselective NSAID. Overall mortality was 56% over the study period. After correcting for severity of HF (based on other prescription data) and comorbid illness, an increased risk of death was associated with most NSAIDs, and was highest with the COX-2 inhibitors and diclofenac. There was no increase with low-dose ibuprofen or naproxen. The hazard ratio (HR) for death was 1.70 for rofecoxib, 2.08 for diclofenac, 1.75 for celecoxib, 1.31 for ibuprofen (all doses), and 1.28 for naproxen (all doses). Baseline pharmacotherapy had no effect on mortality risk. The number of patients needed to treat for 1 year to cause 1 additional death ranged from 9 with rofecoxib to 53 with ibuprofen. The risk of hospitalization for HF was also increased for all NSAIDs, with the HR ranging from 1.16 for ibuprofen to 1.86 for high-dose rofecoxib. Hospitalization for acute MI was increased by a similar amount, from an HR of 1.14 with low-dose diclofenac to 2.43 with higher doses of the same drug.

**Conclusions:** In an unselected cohort of patients with HF, the use of an NSAID was associated with increased mortality as well as increased risk of hospitalization for HF or MI.

**Reviewer's Comments:** With the high overall mortality in this study, even the modest increase in risk conferred by NSAIDs contributes to substantial numbers of deaths. The proportion of patients treated with NSAIDs was striking, even though they required a physician's visit and prescription to obtain—I would guess the proportion is much higher here. I am going to try to start weeding NSAIDs out of the medication lists of my patients with HF and warning them to avoid OTC preparations. (Reviewer-Karen A. McDonough, MD).
In patients with intermittent AF, dronedarone improved a composite of hospitalization for cardiovascular events or death. However, given previous studies, it should not be used in patients with significant heart failure.

**Background:** Previous studies have shown that dronedarone (anti-arrhythmic drug related to amiodarone) helps maintain sinus rhythm and improve rate control compared to placebo in patients with atrial fibrillation (AF). It has been intentionally modified to decrease lipophilicity compared to amiodarone, with the goal to decrease its half-life and potentially minimize its effects on pulmonary and thyroid function.

**Objective:** To determine if dronedarone improves important clinical end points in patients with AF.

**Design:** Multicenter, randomized, double-blind, placebo-controlled trial.

**Participants:** Patients had AF documented in the previous 6 months and at least 1 other risk factor, including age ≥70 years, hypertension (the use of at least 2 medications), diabetes mellitus, previous stroke, transient ischemic attack or embolic event, left ventricular dysfunction (ejection fraction ≤40%), or dilated left atrium. Patients had to have electrocardiograms documenting both AF and sinus rhythm in the previous 6 months (and were excluded if in permanent AF). Exclusion criteria included unstable conditions, class IV heart failure, and glomerular filtration rate (GFR) <10 mL/min.

**Interventions:** Patients were randomized to dronedarone 400 mg twice daily or placebo for a minimum of 12 months.

**Results:** >4600 patients were enrolled (mean follow-up, 21 months). Mean age was 72 years, with nearly 50% being female; 25% were in AF at randomization and only 4% had an ejection fraction <35%. The composite of hospitalization for cardiovascular events or death occurred in 32% of those randomized to dronedarone versus 39% on placebo (HR, 0.76; P <0.0001). No statistical difference in overall mortality was seen, but there were fewer cardiovascular deaths in those on dronedarone versus placebo (2.7% vs 3.9%). Dropout rates were high in both arms (approximately 30%), but not significantly different between groups. Adverse reactions were more common with dronedarone. Bradycardia (3.5% vs 1.2%), QT-prolongation (1.7% vs 0.6%), gastrointestinal events, rash, and creatinine increase (without a change in GFR) were seen more commonly in the treatment group. There were no differences with respect to thyroid and pulmonary adverse events.

**Conclusions:** In patients with AF, dronedarone reduced the likelihood of hospitalization for cardiovascular events or death. Side effects were more common, but dropout rates were similar.

**Reviewer's Comments:** This is certainly an exciting study, as previous trials of anti-arrhythmics in AF have not shown such clinically important end points, but it should be noted that this study lasted <2 years and had high dropout rates, and may underestimate the eventual development of pulmonary and thyroid problems. Also, it included a small number of patients with heart failure. Therefore, given previous concerns regarding the use of dronedarone in patients with severe heart failure, the medication should (when approved) be avoided in such patients. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Atrial Fibrillation

Print Tag: Refer to original journal article
Patients with ED, especially those who are younger, may be at increased risk for future coronary events.

**Background:** Several reports suggest a possible association between erectile dysfunction (ED) and future cardiac events, postulating that ED may be an early manifestation of vascular disease. As both entities share common risk factors (e.g., age, hypertension, and diabetes mellitus [DM]), detailed research is required to understand this relationship.

**Objective:** To investigate the association between ED and subsequent incidence of coronary artery disease (CAD), accounting for common risk factors.

**Design:** Prospective, longitudinal cohort study.

**Participants:** Patients were randomly chosen from an ongoing larger study (Olmstead County Study of Urinary Symptoms and Health Status Among Men) where eligibility included age 40 to 79 years, no neurologic disorders or history of urologic surgery. Participants were followed up regularly with standardized tools that included assessment of erectile function. For this specific ED/CAD analysis, patients had to have a regular sexual partner and no pre-existing heart disease.

**Methods:** Participants were followed up for 10 years, biennially completing reports on erectile function. The Rochester Epidemiology Project, an ongoing surveillance program, was then used to identify patients who developed CAD (i.e., sudden cardiac death, myocardial infarction, or obstructive coronary disease on angiography). Data were collected on potential common risk factors (tobacco use, hypertension, DM, and body mass index). Rates of ED were compared to incident cases of CAD and stratified by age (after adjustment for confounders).

**Results:** 1402 patients (median age, 55 years) were included. Baseline prevalence of ED was 2.4% for age 40 years, 5.6% for age 50 years, 17% for age 60 years, and 39% for age 70 years. For every 2 years of the study, roughly 5% of men subsequently developed ED. New-incident CAD was identified in 11% of participants over the 10 years. After adjustment, the presence of ED was significantly associated with development of CAD, with hazard ratios similar to those of hypertension and DM. Broken down by age, younger ED patients had a much higher incidence (nearly 50x) of CAD than those without ED. By age 70 years, ED had little impact on likelihood of CAD.

**Conclusions:** ED appears to be a risk factor for subsequent development of CAD, especially for men age 40 to 49 years.

**Reviewer's Comments:** This study adds to a *JAMA* report suggesting ED may be a predictor of future coronary events. The authors point out that this may, in fact, be different manifestations of the same disease, with the smaller vessels of the penis affected earlier. Endothelial dysfunction may also play a role. Maybe it is time to think of ED as a risk factor for heart disease and consider being more aggressive in risk factor modification. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Coronary Artery Disease

Print Tag: Refer to original journal article
NVUGIB in Hospitalized Patients

Non-Variceal Upper GI Bleeding in Patients Already Hospitalized for Another Condition.
Müller T, Barkun AN, et al:
Am J Gastroenterol 2009; 104 (February): 330-339

NVUGIB occurs more commonly in inpatients who are sicker, have longer hospitalizations, and have more comorbidities.

Background: Much is known about risks and outcomes associated with non-variceal upper gastrointestinal bleeding (NVUGIB) among outpatients presenting to the emergency department (ED) with acute onset bleeding. Less is known about NVUGIB occurring in patients already hospitalized for another condition. Objective: To compare the incidence, risk factors, and outcomes associated with NVUGIB occurring in outpatients (OPs) compared to inpatients (IPs).

Methods/Participants: This study was part of the Canadian Registry of Patients With Upper Gastrointestinal Bleeding Undergoing Endoscopy. A total of 1878 patients with NVUGIB were selected from 18 community and tertiary care hospitals in Canada. Demographic data, American Society of Anesthesia (ASA) classification, past medical history, medications, and physical examination findings were collected. Principal outcomes were persistent or recurrent bleeding, transfusion requirements, surgery, length of hospital stay, and mortality. Independent predictors of these outcomes were determined by multivariate analysis.

Results: 1395 NVUGIBs occurred among OPs prior to ED presentation; 469 NVUGIBs occurred among IPs after they were hospitalized for another condition. IPs differed from OPs in several important ways: they were sicker (higher ASA class) and had significantly more comorbid conditions (average, 3.1 comorbidities among IPs vs 2.3 among OPs). Endoscopic intervention, endoscopic findings, and transfusion requirements were similar between the 2 groups. IPs required longer hospitalization (7.2 vs 5.4 days) and were more likely to require an ICU stay (although <50% of IPs required ICU stay). Mortality was higher in IPs than OPs (11% vs 3.5%). Among IPs, an increased number of comorbidities and high-risk endoscopic stigmata were associated with an increased risk of persistent or recurrent bleeding; proton pump inhibitor (PPI) use decreased this risk. An increased risk of death was associated with a higher ASA class (3, 4, or 5) at admission, high-risk endoscopic stigmata, and persistent/recurrent bleeding.

Conclusions: IPs who developed NVUGIB after hospitalization for another condition were sicker and had more comorbid conditions than OPs who developed NVUGIB before hospitalization, although endoscopic findings and interventions were similar. IP NVUGIB was associated with longer hospital stays and approximately a 3-fold increased risk of death compared with OP NVUGIB.

Reviewer’s Comments: This interesting trial expands our understanding of NVUGIB occurring during hospitalization for another condition. Previous studies have shown that duration of hospitalization increases the risk of NVUGIB. Important results from this study suggest that illness severity and comorbidities increase the risk of upper GI bleeding, and illness severity and persistent/recurrent bleeding increase the risk of death. Although this study does not help us understand what interventions may reduce the risk of NVUGIB, it is notable that PPI use was associated with a decreased risk. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Non-Variceal Upper GI

Print Tag: Refer to original journal article
Some low-risk patients who present with upper gastrointestinal bleeding may be able to be managed as outpatients.

**Background:** It can be difficult to determine which patients with symptoms of upper gastrointestinal (GI) bleeding could go home safely without being admitted to the hospital.

**Objective:** To develop and test a clinical prediction rule to predict outcomes in upper GI bleeding.

**Methods:** The authors used the Glasgow-Blatchford bleeding score (GBS), which had been derived in a previously published paper. The score incorporates hemoglobin, blood urea nitrogen (BUN), systolic blood pressure, tachycardia, and the presence of melena, syncope, liver disease, and/or heart failure to generate a point score that can range from 0 to as high as 29. Investigators then looked for a reasonable cut-off on the scale to treat people as outpatients. They found that 0 would be the best cut-off. They then tested the hypothesis by implementing the protocol in 2 of their hospital emergency departments (EDs) to allow patients with a GBS score of 0 to go home and follow-up for outpatient endoscopy. They tracked outcomes on these patients to see what would happen.

**Results:** In order to have a GBS score of 0, patients had to have a BUN of <18, a hemoglobin of >13 for men or >12 for women, a systolic blood pressure of >110 mm Hg, a heart rate of <100 bpm, and the absence of melena, syncope, heart failure, and liver disease. Of 491 patients presenting to the ED, 123 (22%) met these criteria; 68% of these patients were allowed to go home. All patients were offered endoscopy as outpatients, but only 40% did so. None of these patients were found to have cancer, varices, ulcers, or any indication for intervention. Of the remaining 60%, none had been readmitted with upper GI bleeding or had died after 6 months of follow-up. Even among those admitted, none required endoscopic intervention.

**Conclusions:** "The GBS identifies many patients presenting to general hospitals with upper GI hemorrhage who can be managed safely as outpatients."

**Reviewer's Comments:** These relatively simple criteria show relatively good performance in identifying a subset of patients who seem to do quite well without hospital admission or even endoscopic intervention. These criteria could be helpful in deciding which low-risk outpatients need to be admitted. As with any clinical prediction rule, I do not think you should trump one's overall clinical judgment: if you believe patients should be admitted, then you should do so regardless of what the rule says. However, in a situation in which your gut tells you the patient should do well at home, these criteria help support that decision in those who meet the criteria. (Reviewer-Christopher L. Knight, MD).

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Keywords: Upper GI

Print Tag: Refer to original journal article
There is little difference between starting with antacids and starting with PPIs when treating dyspepsia.

**Background:** Dyspepsia is common in primary care, but there remains ambiguity about how to best treat it.  
**Objective:** To determine the most effective (and cost-effective) approach to dyspepsia in primary care.  
**Design/Participants:** In this randomized, controlled trial, Dutch patients aged ≥18 years presented to their general practitioner with new-onset dyspepsia. Investigators excluded patients with dysphagia, unintended weight loss, anemia, and hematemesis, as well as those who had undergone an endoscopy in the previous year or used acid-suppressant medication the previous 3 months.  
**Methods:** Patients were randomized to either step-up or step-down treatment protocols. Patients in the step-up protocol initially started with antacids, then advanced to H\textsubscript{2} blockers, and finally to proton pump inhibitors (PPIs). Patients in the step-down protocol started with PPIs, then H\textsubscript{2} blockers, and then antacids. In both protocols, patients were blinded to treatment allocation. Both protocols used the same criteria for step therapy: failure to respond to initial treatment or relapse within 4 weeks after stopping treatment was cause to advance to the next step.  
**Results/Conclusions:** There were no differences in treatment success, quality of life, or adverse events between groups. Roughly one-third of patients were *Helicobacter pylori* positive, with the same 70% response rate as the rest of the cohort. In both groups, roughly 25% of patients responded to the first step, 10% to the second step, and 7% to the third step. There was a small but statistically significant difference in cost. The difference was largely in medication costs, and no difference was seen in either additional medical costs or lost work productivity.  
**Reviewer’s Comments:** The cost difference in this study was small, although it certainly could be significant when multiplied by the large number of people who suffer from dyspepsia. It also might be greater in the United States where medication costs are less regulated. However, I think the most striking result of this study was not the cost savings, but the similarity in outcomes in the 2 groups. My traditional thinking has been that PPIs should be much more potent than antacids and, therefore, should be much more effective in the initial treatment of dyspepsia. These results suggest otherwise. In light of the increasing number of studies suggesting that PPIs may not be as benign as we originally thought, this study certainly leads me to reconsider using antacids and H\textsubscript{2} blockers as initial therapy for dyspepsia. (Reviewer-Christopher L. Knight, MD).  

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**Keywords:** Dyspepsia
Cost-Effectiveness of Genotype-Directed Initiation of Warfarin Therapy

Cost-Effectiveness of Using Pharmacogenetic Information in Warfarin Dosing for Patients With Nonvalvular Atrial Fibrillation.

Eckman MH, Rosand J, et al:

Ann Intern Med 2009; 150 (January 20): 73-83

Genotype-directed initiation of warfarin can reduce the risk of bleeding and the time it takes to achieve therapeutic INRs. This study suggests that the practice is unlikely to be cost-effective at the present time.

Background: Patients with the cytochrome P450 allele CYP2C9 metabolize warfarin more slowly; they are at increased risk of supratherapeutic international normalized ratios (INRs) and take longer to reach stable warfarin dosing. Patients with the vitamin K epoxide reductase VKORC1 group A haplotype require lower doses of warfarin and are at increased risk of supratherapeutic INRs. It remains unknown whether testing for these gene variants is safer or cost-effective when initiating chronic anticoagulation therapy.

Objective: To model the cost-effectiveness of routinely using pharmacogenetic information to determine the initial dose of warfarin for patients with nonvalvular atrial fibrillation (AF).

Methods: This was a decision analysis study comparing pharmacogenetic-based dosing compared with standard induction of warfarin (nomogram based) in a hypothetical patient with AF. Studies estimate that the CYP2C9 and VKORC1 group A genotypes each confer >3-fold increased risk of major bleeding. Pharmacogenetic information reduced the time to first therapeutic INR from 7.5 to 4.8 days and reduced the risk of major hemorrhage by 0.68 (95% CI, 0.22 to 2.06). Bleeding and stroke risk were taken from well-known randomized trials of warfarin in patients with AF. The decision analysis was a Markov model of a hypothetical 69-year-old man at average risk of stroke and no contraindications to warfarin therapy.

Results: Using baseline assumptions, the use of pharmacogenetic information resulted in a gain of 0.0026 quality-adjusted life-years (QALY). The cost of pharmacogenetic-directed dosing added $367 to the cost of induction of warfarin. The marginal cost-effectiveness of pharmacogenetic-directed warfarin dosing was $144,100 per QALY gained. Using a standard discount rate of 3% to adjust for the diminished value of deferred benefits, the adjusted cost-effectiveness was $171,800 per QALY.

Conclusions: Using sensitivity analysis to consider a reasonable range of values in their model, the authors concluded that there was a 10% chance of pharmacogenetic testing resulting in marginal cost-effectiveness of <$50,000 per QALY. Pharmacogenetic testing prior to induction therapy with warfarin resulted in a very small improvement in quality of life (QALY). The estimated cost of this small improvement was high, generally beyond the level that society deems cost-effective.

Reviewer's Comments: Decision analyses are helpful in thinking about the utility of new diagnostic tests or therapies. In this case, pharmacogenetic testing was estimated to confer a small benefit and a high marginal cost. It is also important to note that pharmacogenetic testing might delay initiation of warfarin therapy. It may be that cheaper and more rapid tests would favor pharmacogenetic testing. It may also be worthwhile when considering pharmacogenetic-based dosing in patients at higher risk for hemorrhagic complications. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Pharmacogenetics/Warfarin

Print Tag: Refer to original journal article
Be cautious with proton pump inhibitors in patients on clopidogrel; if you need to use one, the safest is pantoprazole.

**Background:** Genetic variants in cytochrome P450 2C19 are known to inhibit clopidogrel's antiplatelet activity. Proton pump inhibitors (PPIs) (except pantoprazole) are known to inhibit 2C19.

**Objective:** To evaluate the correlation between PPI use and worse outcomes in patients taking clopidogrel after myocardial infarction (MI).

**Design:** Case-control study.

**Participants:** 734 patients with recurrent MI within 90 days and 2057 control subjects in Ontario, Canada.

**Results:** The odds ratio (OR) was 1.27 for recurrent MI in all patients using PPIs along with clopidogrel. No increased risk was found in patients using pantoprazole, and the OR was 1.40 in patients using other PPIs. Although the relative risk increase appears to be modest, an approximation of the absolute risk increase is about 2%, which is close to the expected benefit of clopidogrel.

**Conclusions:** The concurrent use of PPIs decreases clopidogrel's antiplatelet effect and increases the short-term risk of recurrent MI.

**Reviewer's Comments:** This study suggests that the concurrent use of PPIs other than pantoprazole substantially decreases or eliminates the benefit of using clopidogrel after MI. However, one substantial limitation of applying this study to a U.S. population was the low rate of intervention. Only 13% of patients had percutaneous intervention during their initial hospitalization. This probably reflects differences in health care delivery in Ontario, where <10% of acute care hospitals have the ability to do coronary interventions. Based on the results of other trials, it is quite possible that if we repeated this study in a population in which interventions (particularly stents) were used more often, the difference between patients who were and were not taking PPIs might be even larger. (Reviewer-Christopher L. Knight, MD).

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Keywords: Clopidogrel

Print Tag: Refer to original journal article
Patients with certain cytochrome P-450 variants have less metabolism of clopidogrel and are at increased risk for poorer clinical outcomes.

**Background:** The use of clopidogrel, along with aspirin, has become the standard of care for many cardiac patients. However, recurrent events, including stent thrombosis, continue to be an important clinical problem. Clopidogrel is known to require transformation by cytochrome P-450 (CYP) to its active metabolite. As the alleles coding for P-450 are polymorphic, there has been interest in identifying genetic patterns that may affect response to clopidogrel.

**Objective:** To evaluate the association "between functional genetic variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel."

**Methods/Participants:** In the first part of this report, 162 healthy volunteers who had been given various doses of clopidogrel were evaluated. Genotypes were determined, and both the concentration of active clopidogrel metabolite and the degree of platelet inhibition were measured. In the second part, data were extracted from a large study (TRITON-TIMI 38) in which clopidogrel was used for acute coronary syndromes. Genotyping was performed on samples, and subsequent clinical outcomes were compared to the various CYP alleles.

**Results:** In the analysis of healthy volunteers, roughly one-third had at least 1 allele associated with reduced function. Not surprisingly, the slow metabolizers had the lowest levels of active drug and the least platelet inhibition. In the clinical trial, 27% of participants had a reduced-function CYP allele. Those with at least 1 reduced function allele had poorer clinical outcomes, meeting the primary outcome of death from cardiovascular disease, myocardial infarction, or stroke at higher rates than those without such an allele (12% vs 8%). Also, stent thrombosis was more common in the reduced function allele groups (2.6% vs 0.8%).

**Conclusions:** Carriers of reduced function CYP variants have less platelet inhibition and lower active metabolite levels than noncarriers. Carriers also have poorer clinical outcomes, potentially because of lower levels of platelet inhibition.

**Reviewer's Comments:** Although not yet generally available, the future of pharmacology is clearly going to involve better understanding of individual responses to medications. This study is another suggesting that there is great variability in the metabolism of medications, and that these variants are quite common. Someday, perhaps not far in the future, genotyping of metabolism pathways such as CYP will become routine practice. Unfortunately, it is not entirely clear how we would use this information. For example, should we give higher doses of clopidogrel to those with slower metabolism? Until these types of questions are answered, it is difficult to endorse widespread use. However, further research should provide more answers. (Reviewer-Mark E. Pasanen, MD).

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**Keywords:** Clopidogrel

**Print Tag:** Refer to original journal article
The increased risk of breast cancer seen in women on hormone therapy quickly declines to baseline values with cessation of treatment.

**Background:** Initial reports from the 2002 Women's Health Initiative (WHI) showed increased risk of breast cancer in women treated with combined estrogen/progestin therapy, which led to dramatic decreases in hormone use in the United States. Shortly thereafter, breast cancer rates also began to decline. To completely understand the risks of hormone therapy (HT), multiple analyses of the WHI have been performed.

**Objective:** To further analyze data from the WHI for temporal trends in the diagnosis of breast cancer, both during the study and in post-intervention analysis.

**Methods:** These analyses were performed on the randomized trial data and the simultaneous observational cohort, taking into account risk factors for breast cancer and frequency of mammography as related to hormone use. The randomized clinical trial looked at >16,000 women (50 to 79 years old) randomized to either combined HT or placebo. The observational study followed >40,000 women with similar entry criteria and collected data on the use of HT, risk factors for breast cancer, mammography use, and new diagnoses of breast cancer.

**Results:** In the randomized clinical trial, the rates of breast cancer in the HT arm were slightly lower over the first 2 years. However, rates of breast cancer increased steadily over the 5-year time interval, resulting in an increased risk seen at the study's termination (HR, 1.26). More than 15,000 women had data collected after the study was terminated (at which time women had been instructed to stop their appointed treatment). Over the following 2.5 years, there was a steady decline in breast cancer rates, with no differences in other risk factors or mammography. After 2.5 years, adjusted breast cancer rates were similar to those at study onset. As for the observational data set, women taking HT had, on average, a longer duration of hormone exposure than those in the randomized trial. Therefore, breast cancer rates were steady across the early parts of that study, with those on HT having roughly twice as many breast cancers. Slightly more mammograms were performed in those on HT, but not nearly enough to explain these differences. As HT use declined, breast cancer rates declined.

**Conclusions:** The increased risk of breast cancer seen in women taking HT in clinical and observational analyses quickly returned to baseline values with the cessation of HT. This decline cannot be explained by changes in mammography use.

**Reviewer's Comments:** At this point, there seems to be little doubt that combined HT increases the risk of breast cancer. In the first 2 years of treatment, however, no significant differences were seen in those who were relatively hormone naïve. After a few years, risk clearly increases, and declines quickly with cessation of treatment. (Reviewer-Mark E. Pasanen, MD).

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**Keywords:** Breast Cancer

**Print Tag:** Refer to original journal article
Women with a history of childhood cancer and chest radiation require earlier breast cancer screening than those without this history.

**Background:** Women who receive chest radiation for the treatment of cancer at a young age are at increased risk of early breast cancer. Recommended breast cancer screening for this group is an annual mammogram beginning at age 25 years or at least 8 years after the chest radiation. A woman treated at age 20 years with chest radiation therapy for lymphoma would begin mammogram screening at age 28 years.

**Objective:** To assess compliance with these screening recommendations.

**Design:** Case-control study.

**Methods:** The Childhood Cancer Survivor Study is a cohort of long-term survivors of childhood cancer diagnosed between 1970 and 1986. Women aged 25 to 50 years who had a history of chest radiation for childhood cancer were randomly selected to complete questionnaires. Women with childhood cancer but no chest radiation and siblings of study participants comprised the age-matched comparison group. A screening mammogram within the previous 2 years was the primary outcome.

**Results:** 551 women with a history of radiation therapy participated and made up the study group. These women were matched to 562 women with childhood cancer but no radiation, as well as 622 siblings. In women aged 25 to 39 years, 36.5% of study subjects had screening mammograms compared to 15.5% of those with other childhood cancers and 10.6% of siblings, representing the general population. Almost half of the 25- to 39-year-old study group had never had a mammogram; 76.5% of study subjects with chest radiation who were aged 40 to 49 years reported recent mammograms. The most common reasons these women did not have mammogram screening were lack of perceived risk and failure of physicians to recommend screening.

**Conclusions:** Physicians and patients need better education regarding the increased risk of breast cancer and screening recommendations in this specific patient population.

**Reviewer's Comments:** As treatment for childhood cancer improves, physicians will see more adults who have received chemotherapy, radiation therapy, and other targeted treatments that elevate the long-term risk of specific conditions. Keeping up with these ever-changing recommendations can be difficult. Long-term follow-up or survivorship programs are offered at many tertiary hospitals, can be a great resource for patients and physicians, and, based on this study, may be highly underutilized. (Reviewer—Deborah L. Greenberg, MD).

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Keywords: Previous Chest Radiation

Print Tag: Refer to original journal article
"Hospital at Home”—Better Care for Acutely Ill Older Patients?

Comparison of Functional Outcomes Associated With Hospital at Home Care and Traditional Acute Hospital Care.

Leff B, Burton L, et al:


Substituting "hospital at home" care for traditional acute care in the hospital improves functional outcomes for acutely ill older adults.

Objective: To determine if a "hospital at home" (HaH) intervention for acutely ill older adults improves functional outcomes relative to hospitalization.

Design: Nonrandomized clinical trial.

Participants: 214 community-dwelling older adults requiring acute hospital care for pneumonia, cellulitis, or exacerbations of congestive heart failure or chronic obstructive pulmonary disease.

Methods/Interventions: Eligible patients were offered hospital admission or HaH care. The latter involved ambulance transport home, initial one-on-one care by an HaH nurse (mean, 17 hours), followed by at least daily nurse and physician visits. Outcome measures were changes in self-reported activities of daily living (ADL) and instrumental activities of daily living (IADL) scores from 1 month before admission to 2 weeks afterward.

Results: 84 subjects received HaH care, and 130 were admitted to an acute care hospital. Mean subject age was 77 years. Patients electing HaH had lower baseline functional status but otherwise did not differ significantly from patients choosing hospital care in measures of severity of acute illness, underlying health problems, or demographics. Patients treated at home had small but statistically significant improvements in IADL scores compared to hospitalized patients. More HaH patients than hospitalized patients had improvements in functional abilities (ADL scores improved in 45% vs 25%, IADL scores in 46% vs 17%), and less experienced functional decline (ADL decline, 21% vs 31%; IADL, 33% vs 43%), although the differences in ADL scores did not reach statistical significance ($P=0.10$).

Conclusions: HaH care was associated with modest improvements in IADL abilities and a trend toward better ADL function relative to hospital-based care.

Reviewer’s Comments: Previous studies indicate that HaH care for older patients with acute medical illness can provide high-quality care while minimizing iatrogenic complications, reducing caregiver stress and costs, and increasing patient and caregiver satisfaction. This study adds probable modest improvements in functional abilities to the potential benefits of caring for acutely ill older adults in their homes. Potentially significant study limitations include that only one-third of hospitalized patients provided data regarding changes in their functional status, the use of self-reporting to ascertain functional abilities, and the possibility of selection bias whereby patients who chose to be cared for at home were less ill. Study data that patients cared for at home were, in fact, more functionally impaired at baseline and had more comorbid conditions and higher measures of acute illness are reassuring that selection bias was not a major issue. The HaH care model has the potential to provide equivalent medical care to older adults while possibly better preserving functional status, and warrants further study. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Hospital at Home Care

Print Tag: Refer to original journal article
Inability to Perform ADLs While Hospitalized Is Poor Prognostic Sign

Recovery of Activities of Daily Living in Older Adults After Hospitalization for Acute Medical Illness.

Boyd CM, Landefeld CS, et al:

J Am Geriatr Soc 2008; 56 (December): 2171-2179

Older adults discharged with new activities of daily living deficits have poor prognosis for recovery and high 1-year mortality

**Background:** Older adults hospitalized for acute medical problems often develop new disabilities in activities of daily living (ADLs).

**Objectives:** (1) To describe functional outcomes in the year after discharge; (2) to compare outcomes in older adults discharged with and without new ADL deficits; (3) to identify factors associated with a poor prognosis.

**Design:** Prospective observational study.

**Participants:** 2279 adults aged ≥70 years who were nonelectively admitted to a general medical service.

**Methods:** ADLs were determined by self-reporting of abilities 2 weeks before admission, at discharge, and at 1, 3, 6, and 12 months after discharge.

**Results:** 35% of hospitalized older adults were discharged with a new ADL disability. Patients with new ADL deficits were older (mean age, 82 vs 78 years), had longer hospital stays (8 vs 5 days), and had more baseline functional disabilities than persons discharged without new deficits. One year after hospitalization, 41% of patients discharged with new ADL disabilities had died, 29% were alive but had not regained prior function, and only 30% had returned to baseline function; 62% of patients who recovered baseline function did so within 1 month. Failure to recover by 1 month was associated with a worse prognosis. Less than 15% of persons with dementia, cancer, or very advanced age (≥90 years) and new deficits at discharge returned to their baseline function.

**Conclusions:** Patients discharged from the hospital with new disabilities in ADLs are at high risk for poor outcomes.

**Reviewer's Comments:** Hospitalization for acute medical illness often precipitates a decline in functional abilities. Patients who develop such declines tend to be older, sicker, and likely more vulnerable to the "functional stress test" that occurs with acute illness and hospitalization. Functional decline in basic activities of daily living during hospitalization is likely a marker of frailty and vulnerability that portends a poor prognosis. The authors suggest that more intensive rehabilitation efforts might help improve recovery rates, and, given the poor prognosis if recovery did not occur by 1 month, suggest focusing such efforts on the first month after hospitalization. Data indicating that therapy intensity is related to gains in mobility and ADLs make this recommendation reasonable, but further information is needed on the best way to deliver care and rehabilitation services after hospitalization to maximize functional outcomes. Providers should be aware of the prognostic importance of new ADL deficits at the time of hospital discharge. For some patients, particularly those with other negative prognostic factors (dementia, cancer, very advanced age), their functional decline may be a sign that they are nearing the end of their lives, and palliative care interventions may be more appropriate than efforts aimed at restoring function. (Reviewer-Jeff Wallace, MD, MPH).

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**Keywords:** Hospitalization

Print Tag: Refer to original journal article
Although mortality after MI is substantially higher in nursing home residents relative to community-dwelling elderly, adherence to aspirin and β-blocker treatment guidelines does reduce mortality.

**Background:** The appropriateness of applying clinical practice guidelines (CPGs) to frail and/or institutionalized older adults has been questioned because CPGs are generally derived from studies in younger, healthier populations.

**Objective:** To investigate the applicability of treatment guidelines to the care of nursing home (NH) patients who experience an acute myocardial infarction (AMI).


**Participants:** 8151 NH and 119,012 community-dwelling patients hospitalized for AMI.

**Methods:** Adherence to CPGs for the early administration of aspirin and β-blockers during the AMI hospital stay were investigated among NH and community-dwelling patients. Patients were divided into 3 eligibility groups for these medications: ideally eligible, eligible, or intervention contraindicated.

**Results:** NH patients were older (82 vs 76 years), sicker (higher APACHE scores), and more often had do-not-resuscitate (DNR) orders (55% vs 18%) than community-dwelling patients. Mortality rates were higher in NH residents than in community-dwelling elderly (40% vs 18% at 30 days and 65% vs 31% at 1 year; \(P < 0.001\)). Among patients deemed ideally eligible to receive aspirin or β-blockers, fewer NH than community-dwelling patients received aspirin (69% vs 86%) or β-blockers (44% vs 62%). Mortality at 30 days was lower for ideally eligible NH patients who received medications compared to those who were ideally eligible but did not receive aspirin (26% vs 49%) or β-blockers (19% vs 35%) \(P < 0.001\).

**Conclusions:** NH patients were less likely to receive aspirin and β-blockers after AMI, but those who did had substantially lower 30-day mortality rates, suggesting these CPGs have utility in NH patients.

**Reviewer’s Comments:** Although the authors suggest their study findings support applying CPGs for aspirin and β-blockers to NH patients after MI, selection bias rather than actual benefits of aspirin or β-blockers could explain their results. The NH patients were quite old and ill, >50% had DNR orders, and mortality rates were high after AMI regardless of treatment. Clinicians may have decided not to add aspirin or β-blockers as extended survival might not have been consistent with patient/family care preferences. Therefore, I do not view these results as clearly supporting that aspirin and β-blocker CPGs can or should be readily applied to NH residents. I agree with the authors’ call for further study of the factors that may have guided decisions not to provide these medications to reportedly ideally eligible NH patients. Whether the study findings represent inappropriate disparities in the care or rational decision making remains to be determined. In the interim, I do not believe that clinicians’ decisions about following these CPGs in NH patients should be used as measures of quality of care or as pay-for-performance measures, as some have proposed. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Nursing Home Patients

Print Tag: Refer to original journal article
Slow gait speed, a reliable and easily obtained measure, is a key indicator of frailty in older adults.

**Background:** Frailty is a geriatric syndrome associated with adverse clinical outcomes, but there is no clear consensus regarding the criteria to identify frailty. Fried et al proposed a frailty "phenotype" defined as having 3 of the following criteria: slow gait speed, low physical activity, weight loss, self-reported exhaustion, and muscle weakness.

**Objective:** To determine the independent prognostic effect of each of the 5 Fried frailty criteria along with 2 other potential frailty criteria (cognitive impairment and depression symptoms) on adverse clinical outcomes.

**Design/Participants:** Prospective cohort study of 754 community-dwelling adults aged ≥70 years initially without disabilities in 4 activities of daily living: transfers, walking inside home, dressing, and bathing.

**Methods:** Potential frailty criteria definitions were slow gait speed (requiring >10 seconds to walk 10 feet back and forth), low physical activity per score on the Physical Activity Scale for the Elderly, weight loss >10 pounds in the past year, self-reported exhaustion, muscle weakness by grip strength, cognitive impairment (Mini-Mental Status Examination score <24), and depressive symptoms according to the score on the depression scale. Associations between these factors and changes in functional status, long-term nursing home (NH) stay, injurious falls, and mortality were evaluated over 7.5 years.

**Results:** Mean subject age was 78 years; 90% of subjects were white, and 65% were female. Fifty-four percent had a weak hand grip, 43% had a slow gait speed, and prevalence rates for the remaining frailty criteria ranged from 10% to 30%. Over 7.5 years of follow-up, 38% of subjects died and 52% developed chronic disability. Slow gait speed was the only significant predictor of injurious falls (HR, 2.2) and was the strongest independent predictor of chronic disability (HR, 3.0) and long-term NH stay (HR, 3.9). Low physical activity was the strongest predictor of death (HR, 2.2). Only slow gait speed, low physical activity, weight loss, and cognitive impairment were independently associated with adverse outcomes.

**Conclusions:** Low physical activity, weight loss, cognitive impairment, and slow gait speed appear to be valid indicators of frailty.

**Reviewer's Comments:** Many clinicians believe they know frailty when they see it, but developing working criteria to define frailty is important for research and clinical application. Although researchers may continue to struggle to find consensus, slow gait speed appears to be an easily obtainable measure with immediate clinical utility, predicting a 3- to 4-fold increased likelihood of chronic disability or NH stays, and a 2-fold increased risk of injurious falls or death. If the frailty syndrome is potentially modifiable, the first step toward improving outcomes is to identify patients at risk. To that end, clinicians might consider checking if their patients require >10 seconds to go back and forth over a 10-foot course. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Frailty Criteria

Print Tag: Refer to original journal article
Which Men Should Be Screened for Osteoporosis?

Using the Osteoporosis Self-Assessment Tool for Referring Older Men for Bone Densitometry: A Decision Analysis.

Ito K, Hollenberg JP, Charlson ME:

J Am Geriatr Soc 2009; 57 (February): 218-224

It is cost effective to risk-stratify older men for osteoporosis screening and treatment using the Osteoporosis Self-Assessment Tool.

**Background:** Although relatively common and clinically significant, the problem of osteoporosis in men is under recognized and under treated. Recent guidelines from the American College of Physicians recommend that clinicians assess risk factors for osteoporosis in older men and obtain bone density studies in men at increased risk. However, the utility and cost-effectiveness of various risk assessment strategies were not specifically addressed.

**Objective:** To compare benefits and costs of universal bone densitometry for all men at age 70 to a risk-stratifying strategy using the Osteoporosis Self-Assessment Tool (OST) to determine which older men should receive bone density testing.

**Participants/Methods:** A Markov decision model was used to compare benefits and costs of no bone densitometry versus selective bone densitometry using the OST versus universal bone densitometry in a hypothetical cohort of community dwelling 70-year-old white men. An OST score of -2 or less was used to identify high-risk men (OST score = [weight in kg - age] x 0.2).

**Interventions:** Predicted benefits of 5 years of alendronate therapy for older men screened and subsequently diagnosed with osteoporosis.

**Results:** Selective bone density testing using the OST cost $86,500 per quality-adjusted life year (QALY) gained. Universal screening of all men at age 70 cost an additional $421,000 per QALY gained compared to the selective screening strategy. Screening men at age 84 using the OST was more effective and less costly than no bone density screening. An OST score of -2 was the most cost effective cut off to determine if bone density screening should be pursued.

**Conclusions:** Using an OST score of -2 to risk-stratify which older men are candidates for bone densitometry and then treating men diagnosed with osteoporosis with generic alendronate was reasonably cost effective, while universal bone density testing at age 70 years is not.

**Reviewer's Comments:** Although cost-effectiveness studies utilizing Markov analytical models can be daunting to read, this study presented clear model assumptions and conducted sensitivity analyses that were understandable and had clinical relevance. Costs <$100,000 per QALY gained are generally viewed as acceptable from a societal standpoint so I agree with the author's conclusion that using an OST score of -2 to determine if bone density screening is appropriate is reasonably cost effective while universal screening of 70-year-old men is not. A key caveat is that there is currently insufficient evidence to prove that bisphosphonate therapy significantly reduces the risk of nonvertebral fractures in men, so it remains to be determined if the model assumption that alendronate therapy reduces nonvertebral fractures in older men by roughly 25% is valid or not. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Older Men

Print Tag: Refer to original journal article
Glycemic control helps explain some, but not all, of the impact of diabetes on cognitive decline.

**Background:** Diabetes is associated with a higher risk for mild cognitive impairment and dementia. Whether this relationship is due to diabetic control or other mechanisms is unclear.

**Objective:** To determine the role of glucose control in the cognitive function of type 2 diabetics.

**Design:** The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is a randomized control trial of blood pressure as well as glucose and lipid control in 10,251 type 2 diabetics with HgbA1c ≥7.5% and increased cardiovascular risk. The Memory in Diabetes (MIND) sub-study looks at the decline in cognitive function in 2977 of these patients over the age of 55 years. This particular analysis is a cross-sectional study.

**Methods:** Patients underwent a baseline battery of 4 cognitive tests including the Mini Mental Status Examination (MMSE), the Rey Auditory Verbal Learning Test, the Digit Symbol Substitution Test, and the Stroop Test. They also had their baseline glucose control measured. Statistical analyses were adjusted for other known factors that influence cognitive function including cardiovascular disease (CVD), hypertension, hyperlipidemia, alcohol consumption >3 drinks per week, neuropathy, educational level, and prior or current depression.

**Results:** Of the 2977 participants, 47% were women and the average age was 62.5 years. Mean HgbA1c was 8.3% and fasting plasma glucose (FPG) was 175.5 mg/dL. There was a statistically significant relationship between baseline HgbA1c and worse age-adjusted scores on all 4 of the cognitive tests. This relationship persisted throughout most, but not all, of the mathematical adjustments. There was not a relationship between FPG and cognitive test scores.

**Conclusions:** Long-term glucose control as measured by HgbA1c impacts cognitive function in older type 2 diabetics, but does not explain fully the increased risk in these patients.

**Reviewer's Comments:** The results of this study, although statistically significant, were not necessarily clinically significant. The decline in age-adjusted MMSE for each 1% rise in HgbA1c was 0.20 (scale, 0 to 30). This study emphasizes that the relationship between diabetes and adverse outcomes is complex and not fully explained by a single factor. Diabetes control is a modifiable risk factor that may help reduce the risk for cognitive decline in addition to renal, ophthalmologic, and cardiovascular events. (Reviewer-Deborah L. Greenberg, MD).

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Keywords: Glycemic Control

Print Tag: Refer to original journal article
ONJ With Alendronate for Osteoporosis

Sedghizadeh PP, Stanley K, et al:

ONJ presents with exposed, devitalized bone that may be asymptomatic initially.

**Background:** Osteonecrosis of the jaw (ONJ), characterized by exposed and devitalized bone of the maxilla or mandible, has been increasingly recognized as a complication of bisphosphonate therapy, primarily in cancer patients receiving the drugs intravenously. The inciting event for ONJ is usually dental extraction, although periodontal disease and denture trauma have also been implicated. The incidence with oral alendronate, widely used for osteoporosis, has been thought to be low. The American Dental Association has not recommended any specific counselling or change in dental therapy for alendronate-treated patients.

**Objective:** To describe a single institution’s experience with ONJ in patients taking oral alendronate.

**Design:** Retrospective cohort study.

**Participants:** Unselected patients of the University of Southern California Dental Clinic.

**Methods:** An electronic record review was performed to identify patients treated with alendronate, patients with ONJ, and all patients having dental extractions. ONJ was staged as Stage 1 (asymptomatic exposed, necrotic bone), Stage 2 (exposed necrotic bone associated with pain and infection), or Stage 3 (exposed, necrotic bone with pain and infection plus extraoral fistula, pathologic fracture, or extensive osteolysis).

**Results:** 13,730 patients were seen in the clinic. Of these, 208 reported they took alendronate, and 9 of these (all longstanding patients of the dental school, and none referred because of ONJ) developed Stage 2 or 3 ONJ. The ONJ patients were all women ranging from 63 to 80 years old, and all had taken alendronate for at least 1 year for osteoporosis (dose, 70 mg/week). The inciting event was tooth extraction in 4 patients and denture trauma in 5. Overall, one-third of the 13,000 patients seen in the clinic and one-third of the 208 alendronate patients had dental extractions. However, 4 of the 66 alendronate patients developed ONJ after the extraction and none of the untreated patients did.

**Conclusions:** Oral alendronate is associated with ONJ after dental extractions or dental trauma.

**Reviewer's Comments:** In patients treated with oral bisphosphonates, tooth extractions should be avoided unless necessary (this seems to me to be good general advice). If extraction is needed, the authors suggest that top notch dental hygiene and oral chlorhexidine rinses pre- and post-procedure may help prevent ONJ. In practice, I will ask a patient about recent dental follow-up and look for major dental problems before electively starting a bisphosphonate and ask her to make sure her dentist knows about her treatment before procedures are performed. (Reviewer-Karen A. McDonough, MD).

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Keywords: Oral Bisphosphonates

Print Tag: Refer to original journal article
Hospitalization for syncope remains expensive, particularly if a cardioverter-defibrillator is placed.

**Background:** Modern studies on the epidemiology, evaluation, and outcomes associated with syncope date to the early 1980s. It is likely that the evaluation and treatment of syncope is evolving over time.

**Objective:** To describe the rate of hospitalization, mortality rate, and costs of hospitalization for syncope in 2000 to 2005.

**Methods:** The authors utilized the National Inpatient Sample (NIS), a database drawn from 20% U.S. acute care hospitals in >35 states nationwide. Patients primarily admitted for syncope (ICD-9 780.2) from 2000 to 2005 were the study sample. This diagnostic code excludes patients with carotid sinus hypersensitivity and orthostatic hypotension. Also excluded were other causes of loss of consciousness, including seizure, head injury, intoxication, and psychogenic causes. The authors collected comorbidities, costs of hospitalization, and outcomes.

**Results:** 305,932 patients were included in the cohort of patients admitted for syncope; their average age was 69 ± 17.7 years and <10% were <40 years of age. The most common comorbidities were orthostatic hypotension (3.4%) and cardiac arrhythmia (2.7%). The average length of stay was 2 days. The rate of hospital admission for syncope was 0.8 to 0.93 admissions per 1000 person-years; syncope accounted for 0.63% of all hospital admissions. The in-hospital mortality rate for patients admitted with syncope was 0.28%. Not surprisingly, elderly patients and those with more comorbidities had higher mortality rates. Among the 300,000+ patients (23 received pacemakers and 734 had cardioverter-defibrillators placed during hospitalization), there was an increase in placement of cardioverter-defibrillators over the course of the study. The median cost of hospital admission was $8579 (interquartile range, $5247 to $14,137). For patients receiving cardioverter-defibrillators, the median cost was $77,917 (range, $58,478 to $107,822).

**Conclusions:** Rates of admission to the hospital for syncope were lower compared to previous studies. The in-hospital mortality of syncope is low (0.28%), and older and sicker patients have higher mortality rates. Costs of hospitalization for syncope are high, particularly for patients who receive pacemakers or cardioverter-defibrillators.

**Reviewer's Comments:** The most striking finding was the lower rate of admission for syncope compared with historical studies. By comparison, the incidence of visits to the emergency department for syncope has been relatively stable, suggesting that a smaller percentage of patients are being admitted with syncope at the current time. Given the relatively low mortality rate for patients admitted with syncope and how much is known about identifying patients at risk for cardiogenic syncope, this practice seems justified. Admissions for syncope remain expensive, particularly for patients who have cardioverter-defibrillators placed. (Reviewer-Paul R. Sutton, PhD, MD).

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Keywords: Syncope

Print Tag: Refer to original journal article
A multifactorial discharge process may reduce hospital utilization and costs associated with health care, although it is labor intensive.

**Background:** Information is likely to be lost at points of transition in health care, such as at hospital discharge. Discharge summaries or issues that remain outstanding may not be communicated to primary care providers (PCP); patients may not have a good understanding of the nature of their hospitalization, follow up plans, or any changes that may have occurred in their medications. Little is known about how to improve hospital discharge.

**Objective:** To evaluate a multifactorial intervention designed to improve discharge of hospitalized general medical patients.

**Design/Participants:** This randomized trial of a multifactorial discharge intervention took place at Boston University Medical Center from 2003 to 2004. The authors designed a "reengineered discharge" (RED) program consisting of nurse discharge advocates (DAs), a detailed after-hospital care plan (AHCP), and clinical pharmacist telephone contact with patients post-discharge. General medical patients were randomized to usual care at the time of discharge versus RED. The primary end point was hospital utilization, defined as a visit to the emergency department or re-admission to the hospital within 30 days of discharge.

**Results:** 368 patients were enrolled in the usual care group and 370 in the intervention group. In the intervention group, 94% of patients had a primary care appointment at the time of discharge compared with 35% of the usual care group. The intervention group had a lower rate of hospital utilization than usual care, incidence rate ratio of 0.695 (95% CI, 0.515 to 0.937; \( P = 0.009 \)). Participants in the intervention group were significantly more likely to follow up with their PCP following discharge, and required about 90 minutes of nurse time and 30 minutes of pharmacist time per patient. The intervention resulted in savings for the hospital of $412 per discharge.

**Conclusions:** A multifactorial intervention at discharge reduced hospital utilization post-discharge and was associated with cost savings.

**Reviewer's Comments:** Two recent trends in medicine, the growth of the hospitalist movement and the increased attention to quality improvement and patient safety, have converged to shine a light on the importance of communication at transitions of care. The multifactorial intervention described in this study reduced hospital utilization after discharge. It is not clear whether certain aspects of the program would suffice or if the whole package is necessary. Nor is it clear that all patients benefit equally from this sort of intervention. The cost savings reported in this paper are likely to depend on local factors and, importantly, do not include the salaries of the clinical full time employee equivalent necessary to staff this program. This study should prompt other attempts to improve the fidelity of the discharge process. (Reviewer-Paul R. Sutton, PhD, MD).

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**Keywords:** Discharge Planning

**Print Tag:** Refer to original journal article
Background: The U.S. health care system is fragmented, inefficient, and expensive, and improving clinical information technology (IT) is often proposed as an answer.

Objective: To assess the effect of a hospital's use of clinical IT on inpatient mortality, complications, costs, and length of stay (LOS).

Design: Cross sectional study. Methods: 72 urban acute care hospitals from across Texas were selected. Automation (the degree to which clinical information processes are computerized) was assessed by surveying physicians who practiced at each hospital with the Clinical Information Technology Assessment Tool (CITAT). The CITAT divides automation into 4 domains: test results, notes and records, order entry, and decision support. To score highly in a CITAT domain, the clinical information process must be fully computerized, the physician must know how to use it, and must choose the computerized process over any other available alternatives. The final study group was comprised of the 41 hospitals from which at least 5 practicing physicians returned the survey.

Results: After adjustment for patient risk, hospital size and ownership, higher CITAT scores were associated with lower mortality and complications, statistically significantly in some cases. Odds ratios (ORs) for death or complications were calculated for each 10-point increase in CITAT score for the entire population and for subgroups with pneumonia, heart failure, acute myocardial infarction (MI), and coronary artery bypass grafting (CABG). Higher scores for computerized notes and records were associated with lower all-cause inpatient mortality (OR, 0.85). Higher scores for order entry were associated with lower mortality for MI (OR, 0.91) and CABG (OR, 0.45). Higher scores for decision support were consistently associated with lower risk of complications, reaching statistical significance for the entire population (OR, 0.84) and MI (OR, 0.63). Higher scores for test results, order entry, and decision support were all associated with lower mean hospital costs, although there was no clear effect on LOS.

Conclusions: Hospitals with computerized order entry, notes and records, and decision support had lower mortality, complications, and mean hospital costs.

Reviewer's Comments: Although the decreases in mortality, complications, and costs were modest and often did not reach statistical significance, the net impact across hundreds of thousands of hospitalizations would obviously be substantial. There was no negative impact of higher automation in these domains. Interestingly, the study reflects real life experience with automation. The CITAT score was determined by polling a random sample of physicians who practiced at the hospitals, not by talking to the CEO or information technology guys. This study shows that all the money being poured into health IT does not seem to be going down the drain. (Reviewer-Karen A. McDonough, MD).

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Keywords: Clinical Information Technology

Print Tag: Refer to original journal article
More sleep and better sleep efficiency reduce the likelihood of a clinical cold after rhinovirus exposure.

**Objective:** To evaluate the effect of sleep on the likelihood of developing a cold after exposure to rhinovirus.

**Design/Participants:** Prospective cohort study of 153 healthy men and women (21 to 55 years old), with no chronic diseases or medications, no psychiatric problems, normal screening laboratory tests, and low rhinovirus antibody titers.

**Methods:** After acceptance into the study, participants were interviewed daily for 14 days about their sleep the night before, using key items from the Pittsburgh Sleep Quality Index. Questions assessed the duration and efficiency of sleep (the amount of time in bed that was actually spent sleeping). They were then challenged with high titer rhinovirus nasal drops and quarantined in separate rooms for 5 days. A nasal wash for rhinovirus culture was performed daily, and participants scored their cold symptoms and collected their used tissues to estimate daily mucus production; a rhinovirus titer was measured 28 days later. Participants "had a cold" if they had documented infection and clinical symptoms or mucus production.

**Results:** 88% of participants were infected with the rhinovirus, but only about 50% developed a clinical cold, 35% based on objective mucus production and 43% based on symptoms. Mean sleep duration was 7.45 hours (<7 hours in the low tertile, 7 to 8 hours in the middle tertile, and 8+ hours in the high tertile). Mean sleep efficiency was 94% (<92% in the low tertile, 92% to 98% in the middle tertile, and >98% in the high tertile). Low sleep efficiency and duration were associated with developing a cold, with sleep efficiency seeming to account for more of the effect. Participants in the lowest tertile of sleep duration had an odds ratio (OR) of 2.94 for developing a cold compared to the highest tertile, and those in the lowest tertile for efficiency had an OR of 5.5 compared to the highest tertile. Sleep efficiency <85% was considered to be clearly abnormal; the 13 participants in this range had OR of 5.37 for a cold compared to the rest of the sample.

**Conclusions:** Better sleep efficiency and longer sleep duration are associated with lower risk for developing a clinical cold after exposure to rhinovirus.

**Reviewer's Comments:** Almost all participants had evidence of infection with the rhinovirus, but sleep impacted the expression of symptoms. The authors propose that sleep may regulate the expression of cytokines, histamines, and other symptom mediators so that well rested people felt well despite objective evidence of viral infection. Approximately 25% of people get <7 hours of sleep per night; recommending that they increase their sleep to at least 7 hours may decrease their risk of catching a cold. (Reviewer-Karen A. McDonough, MD).
Antidepressants: Some Are More Equal Than Others


Cipriani A, Furukawa TA, et al:

Lancet 2009; (January 29): epub ahead of print

Sertraline and escitalopram offer the best efficacy and tolerability in a multi-drug comparison of antidepressants.

Background: Depression is a common problem, but satisfying to treat in many patients who respond well to therapy. A great deal of mild to moderate depression is handled by primary care physicians.

Objective: To compare efficacy and tolerability of multiple second-generation antidepressants.

Design: Systematic review and meta-analysis.

Methods: The methodology is relatively sophisticated. Simply put, the authors found 117 randomized controlled trials that involved drug-to-drug comparisons among antidepressants. They looked only at "second-generation antidepressants, which included selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors (such as venlafaxine and duloxetine, mirtazapine, and bupropion). They then standardized those trials for treatment response and duration of therapy to enhance comparability, defining acute treatment as 8 weeks. They also tried to capture information on tolerability of the various medications. First, they derived data for all of the head-to-head comparisons they could find, and then used these data to model comparisons that were never studied directly. For example, one study may have compared bupropion to sertraline and another study may have compared citalopram to sertraline; their model allowed them to generate a theoretical comparison between bupropion and citalopram.

Results: Unsurprisingly, the general rule is that one antidepressant is very like another, and there are relatively few major differences between antidepressants in either efficacy or tolerability. However, there are a few interesting exceptions. The 2 drugs that fared the best were sertraline and escitalopram. Both were at least as effective and sometimes more effective than most comparator drugs. Compared to each other, there were no significant differences. By far the worst drug included in the analysis was reboxetine, which compared poorly in both efficacy and tolerability, and is fortunately a drug with which I am not familiar. Other particularly efficacious antidepressants included mirtazapine and venlafaxine, and particularly well-tolerated antidepressants included bupropion and citalopram.

Reviewer's Comments: In many ways, this study reinforces what I already thought, which is that most antidepressants are fairly comparable in terms of efficacy and tolerability. It also helps to validate some subtle biases I held that some drugs were perhaps slightly better or slightly more tolerable than others. For me, the most surprising finding was finding sertraline among the top 2 medications in the study. In my practice, I have tended to use sertraline predominately in the elderly, and to a degree, it fell by the wayside because it was later to go generic than fluoxetine or paroxetine. I may find myself using more sertraline in the future because I read this. (Reviewer-Christopher L. Knight, MD).

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Keywords: Antidepressants

Print Tag: Refer to original journal article
Egg consumption does not increase cardiovascular events in men, but ≥1 egg a day increases the risk of death over 20 years.

**Background**: The average chicken egg is complex containing vitamins, minerals, protein, and 200 mg of cholesterol. As conventional wisdom focused on lowering cholesterol to improve cardiovascular health, eggs became a maligned component of the American diet.

**Objective**: To examine the association between egg consumption and cardiovascular disease.

**Design**: The Physicians' Health Study (PHS) is a double-blind, randomized, placebo-controlled trial assessing low-dose aspirin and β-carotene for the primary prevention of cardiovascular disease and cancer in men. This substudy is a prospective cohort study.

**Methods**: 21,327 U.S. male physicians between the ages of 40 and 85 years were enrolled. Men were healthy without a prior history of cardiovascular disease, cancer, or significant liver or kidney problems. Participants in this substudy of the PHS completed food frequency questionnaires at baseline and every 2 years for 10 years. Subjects were divided into 6 categories based on egg consumption: rarely or never; 1 to 3/month; 1/week; 2 to 4/week; 5 to 6/week; daily; and >2/day. Data on comorbidities for cardiac disease, such as exercise and smoking, were collected at baseline. The primary end point was occurrence of myocardial infarction (MI), stroke, or death.

**Results**: The average age of the population at baseline was 53.7 years. The average egg consumption was 1 egg per week, and the average follow-up was 20 years. In a multivariate analysis, egg consumption was not associated with an increased risk of incident MI or stroke. However, compared to those who never or rarely ate eggs, men consuming ≥7 eggs per week had a 23% increased risk of death (HR, 1.23; 1.11 to 1.36). This risk was greatest in men with diabetes at baseline. Compared to diabetics who did not consume eggs, those consuming 7 eggs per week were twice as likely to die during the follow-up period (HR, 2.01; 1.26 to 3.20).

**Conclusions**: Infrequent egg consumption does not increase the risk of MI, stroke, or death in men. However, an average of ≥1 egg(s) per day does increase the risk for death from any cause, especially in diabetics.

**Reviewer’s Comments**: This study does not support the commonly held notion that eggs are bad for your heart. It does however raise an interesting question about egg consumption and death, especially in diabetics. (Reviewer-Deborah L. Greenberg, MD).

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