Norepinephrine Probably Better Than Dopamine for Shock

Comparison of Dopamine and Norepinephrine in the Treatment of Shock.

De Backer D, Biston P, et al:

N Engl J Med 2010; 362 (March 4): 779-789

In patients with shock (septic, cardiogenic, or hypovolemic), norepinephrine is likely a better first-line vasopressor than dopamine.

Background: Consensus guidelines and expert recommendations suggest that either dopamine or norepinephrine can be used in the treatment of shock, but few randomized trials exist.
Objective: To compare dopamine to norepinephrine as first-line vasopressor therapy in the treatment of shock.
Design: Multicenter randomized head-to-head trial.
Participants/Methods: In multiple European centers patients with shock who needed vasopressor therapy were enrolled between 2003 and 2007. Shock was defined as a mean arterial pressure <70 mm Hg or a systolic blood pressure <100 mm Hg despite getting intravenous fluids (1000 mL of crystalloid) and evidence of hypoperfusion (confusion, low urine output, elevated lactate). Enrolled patients were randomized to dopamine or norepinephrine infusions at standard dosing adjusted as needed. If patients remained hypotensive after maximal dosing, open-label norepinephrine was added.
Results: 1679 patients were enrolled; 62% had septic shock, 17% cardiogenic shock, and 16% hypovolemic shock. There was no difference in 28-day mortality between the dopamine (52.5%) and norepinephrine groups (48.5%; *P* =0.10). There was also no difference in time to shock resolution, rates of ICU death, in-hospital death, or death at 6 and 12 months between the 2 groups. There was no difference in the amount of fluids given or the doses of open-label norepinephrine needed. Arrhythmias were much more common in the dopamine group (24.1% vs 12.4%; *P* <0.001), especially atrial fibrillation. In subgroup analysis, in patients with cardiogenic shock, the 28-day mortality was significantly higher in the dopamine group compared to the norepinephrine group (*P* =0.03 by Kaplan-Meier).
Conclusions: There was no difference in overall mortality between dopamine and norepinephrine in patients with shock but dopamine was associated with an increased risk of arrhythmia and increased mortality in patients with cardiogenic shock.
Reviewer's Comments: There is a long-standing belief that norepinephrine is associated with increased death (thus "Levophed" becoming "Leave-'em-dead"). This well-done study not only debunks that but proves that norepinephrine likely should be our first-line vasopressor in patients with shock that is not fluid responsive. Most guidelines (especially those for septic shock) state we can use either, but this study reveals overall outcomes are no different and rates of arrhythmia are much higher in the dopamine group. In addition, if you are managing patients with cardiogenic shock, dopamine should generally be avoided. (Reviewer-Bradley A. Sharpe, MD).

Keywords: Shock, Vasopressors, Dopamine, Norepinephrine

Print Tag: Refer to original journal article

No Shock -- Early Antibiotics Improve Mortality in Severe Sepsis

Impact of Time to Antibiotics on Survival in Patients With Severe Sepsis or Septic Shock in Whom Early Goal-Directed Therapy Was Initiated in the Emergency Department.

Gaieski DF, Mikkelsen ME, et al:

Crit Care Med 2010; 38 (April): 1045-1053

Appropriate antibiotics should be given within the first hour of early-goal directed therapy for severe sepsis and septic shock in order to maximize mortality benefit.

Background: The high mortality of severe sepsis and septic shock is decreased with early goal-directed therapy (EGDT). The optimal timing of antibiotic administration within this set of interventions, though recommended early in resuscitation algorithms based on existing data, has not been specifically determined.
Objective: To determine the mortality impact of antibiotic timing, when administered with EGDT, for severe sepsis or septic shock.
Design: Single-site retrospective cohort study.
Participants: 261 patients with severe sepsis or septic shock who qualified for EGDT.
Methods: Data were abstracted for enrolled patients, including illness severity, triage time, time of qualification for EGDT, time to initial antibiotics, appropriateness of antibiotics, and time to appropriate antibiotics. Mortality of patients receiving antibiotics at various time points was compared and adjusted for potential confounders. Odds ratios (OR) for mortality were calculated.
Results: All patients received antibiotics in the ED. In total, 56.7% were culture positive; the majority of these received appropriate initial antibiotics. The median time from triage to antibiotics was 119 minutes -- 42 minutes from EGDT qualification. Times from triage and EGDT qualification to appropriate antibiotics were longer -- 127 and 47 minutes, respectively. Overall in-hospital mortality was 31%. There were no significant mortality differences based on presence or absence of culture positivity or receipt of appropriate antibiotics in the ED. Accounting for other confounders, there were no mortality differences based on antibiotic timing from triage or EGDT qualification. However, mortality was decreased in patients who received appropriate antibiotics <1 hour from triage (OR, 0.3) or <1 hour from EGDT qualification (OR, 0.5) as compared with ≥1 hour.
Conclusions: Appropriate antibiotics should be administered in severe sepsis and septic shock within 1 hour of EGDT qualification.
Reviewer's Comments: These study results, though limited by small sample size and single-site data, are in line with Surviving Sepsis Campaign recommendations. They also call into question the room for interpretation regarding antibiotic timing conferred by the ED-SEPSIS Working Group. Current performance measures do not account for the appropriateness of an antibiotic regimen, yet this is where the mortality benefit was found. These results cannot be extrapolated to patients who do not qualify for EGDT. Patients presenting with severe sepsis or septic shock are increasingly the beneficiaries of multiple, simultaneous, evidence-based interventions. This well-done study in which patients received high quality care suggests that early and appropriate antibiotics should be counted among these interventions. This presents an ideal venue for systems improvements. (Reviewer-Jennifer Best, MD).

Keywords: Sepsis, Septic Shock, Early Goal-Directed Therapy, Emergency Care

Print Tag: Refer to original journal article

Earlier Tracheotomy in ICU Patients Does Not Prevent VAP

Early Vs Late Tracheotomy for Prevention of Pneumonia in Mechanically Ventilated Adult ICU Patients: A Randomized Controlled Trial.

Terragni PP, Antonelli M, et al:

JAMA 2010; 303 (15): 1483-1489

In this study, early tracheotomy did not statistically significantly decrease ventilator-associated pneumonia rates compared with late tracheotomy but decreased ventilator and ICU days.

Background: Tracheotomy facilitates secretion management, oral feeding and patient communication and may prevent ventilator-associated pneumonia (VAP), lead to earlier weaning from respiratory support, and reduce sedative use. There is considerable variation in tracheotomy timing and incidence. Impact of timing on outcomes is not known.
Objective: To compare the impact of early tracheotomy (6 to 8 days after intubation) with late tracheotomy (13 to 15 days after intubation) on incidence of VAP.
Design: Randomized controlled trial of 12 Italian ICUs from 2004 to 2008.
Participants/Methods: All adult ICU patients who were mechanically ventilated for acute respiratory failure with a Simplified Acute Physiology Score II 35 to 65 and a Sequential Organ Failure Assessment (SOFA) Score >5 who did not have pulmonary infection (Clinical Pulmonary Infection Score (CPIS) <6) were enrolled. Patients with chronic obstructive pulmonary disease (COPD); neck deformities; history of head, neck, pulmonary or hematologic malignancy; prior tracheotomy; neck soft-tissue infection; or pregnancy were excluded. Patients were randomized to early versus late tracheotomy 48 hours after enrollment if PaO_2 ≤60 mm Hg with FiO_2>0.5 and PEEP >8 cm H_2O and they were not improving from a respiratory standpoint, did not have pulmonary infection, and were not moribund. All analyses were performed on an intention-to-treat basis. Primary outcome was 28-day cumulative VAP incidence. Ventilator-free and ICU-free days, length of stay, long-term care facility at discharge, and mortality were secondary outcomes. All patients were placed in the semirecumbent position; weaning and sedation were adjusted per protocol.
Results: 419 patients were randomized (209 early tracheotomy; 210 late). Mean age was 62 years; approximately 67% were male. In total, 36% to 40% of patients were medical, 49% to 55% surgical, and 9% to 11% trauma in the 2 groups, respectively. All tracheotomies were performed at the bedside. Sixty-nine percent of patients in the early group underwent tracheotomy versus 57% in the late group; 39% in each group experienced adverse events. Fourteen percent (30) in the early tracheotomy group were diagnosed with VAP and 21% (44) in the late group, with a non-significant hazard ratio of 0.66. Ventilator- and ICU-free days, successful weaning rates, and ICU discharge were significantly greater in the early group. There were no significant differences in 28-day or 1-year mortality or in need for long-term care facility at discharge.
Conclusions: Tracheotomy performed after 6 to 8 days of intubation did not result in statistically significant reduction in VAP incidence compared with tracheotomy performed after 13 to 15 days.
Reviewer's Comments: This is a well designed multicenter study involving >400 ICU ventilated patients of relevance to hospitalists who often manage ICU patients. Randomization to early tracheotomy led to more tracheotomies without statistically significantly preventing VAP. Patients in the early trach group had fewer ventilator and ICU days. Additional studies in other populations are necessary to help determine optimal timing of tracheotomy in ventilated ICU patients. (Reviewer-Anneliese M. Schleyer, MD).

Keywords: Tracheotomy, Ventilator-Associated Pneumonia

Print Tag: Refer to original journal article

Risk of Catastrophic Asthma Events Increased By Long-Acting Beta-Agonists

Long-Acting Beta Agonists With and Without Inhaled Corticosteroids and Catastrophic Asthma Events.

Salpeter SR, Wall AJ, Buckley NS:

Am J Med 2010; 123 (April): 322-328

Concomitant use of inhaled steroids with long-acting beta-agonists may not decrease the associated risk of catastrophic asthma events.

Background: Long-acting beta-agonists (LABA) have been shown to increase the risk of intubation and death in asthma. The risk of LABA in association with inhaled corticosteroids has not been well studied.
Objective: To evaluate existing evidence regarding the risk of catastrophic asthma events with LABA, in the setting of variable and concomitant inhaled corticosteroids.
Design: Meta-analysis.
Methods: Studies were identified with key word and manual database searches and review of clinical trial registries. Candidate studies were reviewed and abstracted by 2 investigators. The relevant outcomes were catastrophic asthma events (intubations or death). Where possible, results were pooled and odds ratios (OR) generated. A second analysis accounting for all trials -- those with and without catastrophic events -- was performed to estimate absolute risk increase. Results were also analyzed by subgroup. A sensitivity analysis was performed to account for pooled data from a pharmaceutical company that lacked trial-level information. Studies were randomized controlled double-blind intention-to-treat trials of LABA compared with placebo and studies of LABA with inhaled corticosteroids compared with similarly-dosed inhaled corticosteroids alone. Treatment duration for all studies was ≥3 months and all reported at least 1 catastrophic asthma event.
Results: 10 studies (n=36,588 participants/21,343 patient-years) met inclusion criteria; additional data were provided by GlaxoSmithKline and meta-analyzed as 2 pooled trials. Five trials evaluated LABA with variable corticosteroids; 7 evaluated LABA with concomitant corticosteroids. The overall OR for catastrophic events with LABA versus control was 2.10. For LABA + variable corticosteroids versus placebo, the OR was 1.83. With LABA + concomitant corticosteroids versus corticosteroids alone, the OR was 3.65. Subgroup analysis revealed no significant discrepancies. The calculated absolute risk increase was 3 catastrophic asthma events per 10,000 patients treated over 5 months.
Conclusions: This is the first meta-analysis demonstrating that LABAs are associated with significant risk of asthma intubation and death, even when used with inhaled steroids. The primary limitations of this study were the low rate of catastrophic events and lack of a risk-benefit analysis.
Reviewer's Comments: Hospitalists commonly admit patients with exacerbations of reactive airway disease and asthma. Identification and management of precipitants should remain a high priority. If it is determined that medication escalation is necessary, optimizing a patient's inhaled steroid dose may be an appropriate first step. Salmeterol and formoterol should probably be avoided in most cases in favor of other agents, even if that patient is using concomitant inhaled steroids. In no case should LABA be used in isolation. Consultation with a pulmonologist may be useful. Many patients are already using LABA. Discontinuation of LABAs or other changes in a patient's asthma regimen should ideally occur only after communication with the prescribing physician. (Reviewer-Jennifer Best, MD).

Keywords: Reactive Airway Disease, Asthma, Long-Acting Beta-Agonists, Corticosteroids

Print Tag: Refer to original journal article

Rifaximin May Prevent Recurrent Episodes of Hepatic Encephalopathy

Rifaximin Treatment in Hepatic Encephalopathy.

Bass NM, Mullen KD, et al:

N Engl J Med 2010; 362 (March 25): 1071-1081

In this study, when added to lactulose, rifaximin decreased the risk of breakthrough hepatic encephalopathy and related hospitalization.

Background: Rifaximin has been shown to be superior to lactulose for treatment of acute episodes of hepatic encephalopathy (HE), but its efficacy in maintenance of remission is unknown.
Objective: To evaluate the efficacy and safety of rifaximin, when used with lactulose, in preventing recurrent episodes of acute HE.
Design: Multicenter randomized double-blind placebo-controlled trial.
Participants: Patients >18 years with cirrhosis, ≥2 episodes of acute HE in the previous 6 months, in remission at time of enrollment, and MELD score ≤25 were evaluated. Patients were excluded if transplantation was expected within 1 month or if conditions associated with encephalopathy were present.
Methods: Following screening and observation, patients were randomized to rifaximin 550 mg or placebo twice daily for 6 months; concurrent lactulose administration was allowable. Clinic visits occurred at days 7, 14, and then every 2 weeks to day 168 for assessment of Conn score and asterixis grading, supplemented by telephone contact. The primary end point was time to first dose to breakthrough episode of HE; the secondary end point was time to first HE-related hospitalization. Outcomes were evaluated by subgroup. Data were analyzed on an intention-to-treat basis.
Results: 299 patients were enrolled. The groups were similar at baseline, with similar percentages of patients receiving lactulose. Recurrent episodes of HE were less frequent in the rifaximin group than with placebo (22.1% vs 45.9%; HR, 0.42; *P* <0.001). Hospitalizations were also less frequent (13.6% vs 22.6%; HR, 0.5; *P* =0.01). Safety was similar between the groups. Most deaths occurred in patients with decompensated cirrhosis and were attributable to progression of disease.
Conclusions: In all subgroups, rifaximin use decreased recurrence of HE and hospitalizations over 6 months as compared with placebo.
Reviewer's Comments: Recognition of patients who have had recurrent episodes of HE is a role for the hospitalist and consideration should be given to rifaximin initiation prior to discharge. This study suggested superiority of rifaximin, as compared with lactulose alone, on the basis of a treatment effect seen within 28 days versus 4 months, but recall that many patients with HE are challenged by medication compliance. To add rifaximin to lactulose may further tax their capabilities, though the side effect profile may be more tolerable. (Reviewer-Jennifer Best, MD).

Keywords: Hepatic Encephalopathy, Cirrhosis Complications, Oral Antibiotics

Print Tag: Refer to original journal article

Does Your Patient With DVT Have a Silent PE as Well?

Silent Pulmonary Embolism in Patients With Deep Venous Thrombosis: A Systematic Review.

Stein PD, Matta F, et al:

Am J Med 2010; 123 (May): 426-431

Conservatively 25%, and as many as 32%, of patients presenting with a symptomatic deep venous thrombosis may have a silent pulmonary embolism as well.

Background: Pulmonary embolism (PE) is a potentially fatal disease, but one that often goes undiagnosed.
Objective: To determine the prevalence of asymptomatic PE in patients who are diagnosed with a symptomatic deep venous thrombosis (DVT).
Methods: The authors reviewed the literature for studies in which patients presenting with a DVT had routine screening for a PE, and for whom the presence of an asymptomatic PE was noted. The studies were divided into 2 tiers based on the criteria for the diagnosis of PE. Tier 1 included studies where PE diagnosis was more rigorous, that is by CT pulmonary angiography, conventional pulmonary angiography, or high probability V-Q scan based on accepted published guidelines. Tier 2 studies included those where the PE was diagnosed by V-Q scan with unstated or unvalidated diagnostic criteria. The authors also looked at potential risk factors for asymptomatic PE in the presence of DVT.
Results: 12 tier 1 studies and 16 tier 2 studies met the inclusion criteria. In the tier 1 studies, the prevalence of asymptomatic PE was 27% compared to 37% in tier 2 studies, with a combined prevalence of 32%. When examining the prevalence in proximal DVTs, only the rates of asymptomatic PE in tier 1 and 2 studies was 26% and 54%, respectively, with the combined prevalence of 32% -- the same as that for combined proximal and distal DVTs. However, larger perfusion defects were seen in patients with more proximal thigh or pelvic vein DVTs. There was also suggestion from the articles reviewed that recurrent PE was more common in those who had a silent PE diagnosed with their DVT than those who didn't.
Conclusions: Approximately 32% (27% at the most conservative estimate) of patients diagnosed with a DVT will also have a silent or asymptomatic PE.
Reviewer's Comments: The authors cite several valid reasons why in certain cases it might be appropriate to know if a patient has both a DVT and an asymptomatic PE. Firstly, it would give a baseline to future imaging studies if the patient were to become symptomatic, and it would prevent misdiagnosis of this as a new PE and thus a failure of anticoagulation therapy. Second, it also might push you to hospitalize a patient who you would otherwise send home from the ED with low-molecular-weight heparin. Lastly, studies suggest that recurrent PE during treatment for DVT is more frequent in those patients who had a silent PE with their initial DVT. Whether the knowledge of a silent PE is worth the cost and radiation exposure may be a patient by patient decision. (Reviewer-Michelle Mourad, MD).

Keywords: Pulmonary Embolism, Deep Venous Thrombosis

Print Tag: Refer to original journal article

Early Therapeutic Anticoagulation for Acute PE May Be Associated With Lower Mortality

Early Anticoagulation Is Associated With Reduced Mortality for Acute Pulmonary Embolism.

Smith SB, Geske JB, et al:

Chest 2010; 137 (June): 1382-1390

Adult patients with acute pulmonary embolism who received heparin in the emergency department had lower in-hospital and 30-day mortality rates compared with those started on heparin after admission.

Background: Therapeutic dose heparin improves survival in acute pulmonary embolism (PE) and reduces incidence of recurrent venous thromboembolism (VTE). Less is known about the association of timing of initial anticoagulation and time to achieving therapeutic levels with mortality.
Objective: To describe the relationship between anticoagulation timing and mortality.
Design: Retrospective review at a single academic tertiary care center from 2002 to 2005.
Participants/Methods: Adult patients who presented to the emergency department (ED) and were diagnosed with PE were eligible. Those with PE diagnosis prior to arrival or with contraindications to anticoagulation were excluded. All patients were treated with unfractionated IV heparin per weight-based nomogram. Patients were characterized as receiving heparin in the ED (early) or after admission and as achieving therapeutic activated partial thromboplastin time (aPTT) within 24 hours of ED arrival or later. In-hospital and 30-day mortality were primary outcomes. Hospital and ICU length of stay (LOS), hemorrhagic events, and 90-day VTE recurrence were secondary outcomes.
Results: 400 patients were eligible. Median age was 68 years; 49% were men. In total, 19% required ICU admission and 70% (280) of patients received heparin in the ED; 5% (20) received heparin empirically prior to CT diagnosis. Patients who received heparin in the ED were younger with higher Wells scores and less likely to have significant comorbidities, positive D-dimer, or high troponin. Median time from ED arrival to therapeutic aPTT was approximately 11 hours; 86% of patients had a therapeutic aPTT within 24 hours of ED arrival. Overall in-hospital and 30-day mortality rates were 3.0% and 7.7%, respectively. Patients who received early heparin had lower in-hospital (1.4% vs 6.7%; OR, 0.2; P =0.009) and 30-day mortality (4.4% vs 15.3%; OR, 0.25; P <0.001) compared with those started on heparin after admission. Those with therapeutic aPTT within 24 hours trended to lower 30-day mortality (OR, 0.34; P =0.037); the difference in in-hospital mortality was not statistically significant. Early anticoagulation remained predictive of reduced mortality in multiple regression models. Patients who received heparin in the ED had shorter overall and ICU LOS. Overall, 5% of patients had hemorrhagic events on heparin. Anticoagulation timing did not affect hemorrhagic events. Achieving a therapeutic aPTT within 24 hours was associated with decreased risk of hemorrhage (OR, 0.28).
Conclusions: Early therapeutic anticoagulation may be associated with decreased mortality in acute PE.
Reviewer's Comments: This is a well-done single-site retrospective study of relevance to hospitalists who care for many patients with VTE. While results do not prove causality between early anticoagulation and survival, additional prospective multi-site studies of ideal timing of anticoagulation may be warranted (potentially with other therapies). Of note, in this retrospective review only a few patients were empirically started on IV heparin prior to PE diagnosis despite this being standard of care. (Reviewer-Anneliese M. Schleyer, MD).

Keywords: Anticoagulation, Pulmonary Embolism

Print Tag: Refer to original journal article

Higher Heart Rate in Afib May Be OK

Lenient Versus Strict Rate Control in Patients With Atrial Fibrillation.

Van Gelder IC, Groenveld HF, et al:

N Engl J Med 2010; 362 (April 15): 1363-1373

In patients with chronic atrial fibrillation, lenient rate control (goal <110 bpm at rest) was no different for any clinical outcome compared to strict rate control (goal <80 bpm at rest).

Background: Rate control is often the primary goal in atrial fibrillation (afib) and most guidelines recommend strict control. There is very little evidence regarding optimal heart rate goal in persistent afib.
Objective: To compare lenient versus strict rate control in patients with permanent afib.
Design: Randomized trial.
Participants/Methods: In 33 centers in the Netherlands, patients aged <80 years who had afib for >12 months (permanent afib) and whose mean resting heart rate was >80 beats per minute (bpm) were enrolled. Patients were randomized to a lenient control strategy with a target resting heart rate of <110 bpm or a strict control strategy with a target resting heart rate of <80 bpm. Rate was achieved using ≥1 nodal agents (ie, beta-blocker, calcium channel blocker, digoxin). All patients in the strict control group underwent 24-hour Holter monitoring after the target heart rate was achieved.
Results: 614 patients were enrolled, over half of whom were symptomatic at baseline from their afib. The mean heart rate achieved was approximately 85 bpm in the lenient control group and 75 bpm in the strict control group. Nearly all (98%) in the lenient control group achieved the target heart rate while only 75% of patients in the strict control group had a resting heart rate of <80 bpm. Most patients achieve the target through the use of beta-blockers or beta-blockers + digoxin. There was no difference between the 2 groups in the primary outcome of death from cardiovascular causes, stroke, embolism, major bleeding, arrhythmic events, syncope, etc. There was also no difference in all-cause death, control of symptoms, or adverse effects of drugs. But, the strict control patients required many more visits to achieve the target heart rate.
Conclusions: Lenient control is not inferior to strict rate control in patients with chronic afib.
Reviewer's Comments: Hospitalists often manage patients with afib and have to decide on the optimal heart rate prior to discharge. Most expert guidelines recommend strict rate control (<80 bpm). This study, notably limited to patients with permanent chronic afib, reveals that in long-term follow-up there is no difference in any clinical outcome between lenient and strict rate control. Although this is only one study and we probably cannot safely apply this to patients with new afib, it does reveal that we may not need to be as aggressive about rate control. It seems reasonable for patients with afib to try to use nodal agents to achieve a target heart rate of <100 bpm at rest prior to discharge from the hospital. Regarding optimal rate in afib with exertion, we have to await future studies. (Reviewer-Bradley A. Sharpe, MD).

Keywords: Atrial Fibrillation, Rate Control

Print Tag: Refer to original journal article

A Delay in Filling Clopidogrel Rx After DES Placement Is Like Playing With Fire

Delays in Filling Clopidogrel Prescriptions After Hospital Discharge and Adverse Outcomes After Drug-Eluting Stent Implantation: Implications for Transitions of Care.

Ho PM, Tsai TT, et al:

Circ Cardiovasc Qual Outcomes 2010; 3 (May): 261-266

One in 6 patients delays filling a clopidogrel prescription following drug-eluting stent placement and is at increased risk of adverse cardiovascular outcomes.

Background: Clopidogrel is proven to decrease the risk of stent thrombosis following drug-eluting stent (DES) placement. The rate at which patients fill this medication following hospital discharge and the related effect of delays on outcomes are unknown.
Objective: To determine whether patients delay filling clopidogrel prescriptions following DES placement, to establish delay length and whether delay increases risk of death or myocardial infarction (MI), and to identify risk factors associated with delay.
Design: Retrospective cohort study.
Participants: Post-DES patients with a pharmacy benefit plan and no in-hospital bleeding discharged alive from 1 of 3 managed care systems.
Methods: Patient and clopidogrel data were obtained from clinical, administrative, and pharmacy registries. Fill date was initially dichotomized based on discharge day versus all other days. The primary outcome was all-cause mortality or MI. Baseline patient characteristics and outcomes were compared for patients with and without clopidogrel delay. Logistic regression identified factors associated with delay. Secondary analyses recategorized clopidogrel delay as >1, >3, and >5 days post-discharge and evaluated long initial delay as a surrogate for refill delay and the effects of delays for other cardiac medications. In patients who had filled clopidogrel, the association between outcomes and delay in filling a new statin was examined to assess whether effects were clopidogrel-specific.
Results: Of 7402 post-DES patients, 16.3% delayed filling clopidogrel by >1 day. Of these, 13.6% never filled clopidogrel. Patients with delays were older, had greater comorbidity, and a greater number of cardiac medications. Patients with >1 day delay had increased risk of death/MI (14.3% vs 7.9%; P <0.001), with most events occurring within 30 days of discharge. Any delay increased risk of death/MI, as well as death alone. This outcome remained for delays categorized as >1, >3, and >5 days. Initial delay of >7 days predicted refill delay. Increased risk of death/MI persisted when adjusted for delay in filling other medications. In those who filled clopidogrel, statin delay did not predict adverse outcomes.
Conclusions: 1 of 6 patients delayed filling clopidogrel following DES placement, with increased risk of death/MI.
Reviewer's Comments: The adverse effects of prescription delay here are specific to clopidogrel in the setting of DES placement, with a strong pharmacologic basis for the observation. This study likely underreports the true occurrence of delay, as all patients in this cohort had a prescription drug benefit. More generally, these authors provide another frightening perspective on transitions in care. There are many reasons for prescription delays. At the time of discharge, hospitalists should specifically discuss with patients the clinical rationale for specific medications, concrete plans, and financial ability to obtain medications. For higher risk situations such as DES placement, filling certain medications prior to discharge might become standard of care. (Reviewer-Jennifer Best, MD).

Keywords: Transitions of Care, Hospital Discharge, Medication Management

Print Tag: Refer to original journal article

Does Ranking Equal Reputation?

The Role of Reputation in U.S. News & World Report's Rankings of the Top 50 American Hospitals.

Sehgal AR:

Ann Intern Med 2010; 152 (April 20): 521-525

Rankings put forth by the *U.S. News & World Report* may depend more on hospital reputation than more objective measures of quality.

Background: Much is made of the *U.S. News & World Report* hospital rankings published by the magazine every year, but the report has been criticized for weighing reputation too highly in its rankings.
Objective: To understand the role of reputation in the determination of the rankings put forth by the popular news magazine.
Methods: *U.S. News & World Report* uses a combination of structure -- objective measures of the people and resources devoted to care and process -- subjective reputation, and outcomes -- objective measures of mortality and adverse events to formulate their rankings. The author used several statistical methods to determine the influence of reputation -- first, by calculating variation of reputation scores as compared to the variation in more objective measures. Second, the author looked at the distribution of reputation in the top 50 hospitals as compared to 100 unranked hospitals. Third, the author examined the ability of reputation alone to predict the rankings and fourth, determined the association between reputation and the more objective measures of quality.
Results: Reputation varied more widely among the top 50 hospitals than in the objective measures of quality. This serves to give reputation more weight than the more similar objective measures in establishing the hospital rankings. Reputation scores also were not evenly distributed through the rankings, but rather heavily swayed to those in the top 50, demonstrating the relative importance of this variable. Reputation alone was highly predictive of the final rankings with reputation alone predicting 100% of the number one hospitals in each specialty, 97% of the top 5 hospitals in every specialty, and 89% of the top 20 hospitals in every specialty. Reputation was also not reflective of overall quality as it poorly correlated with other quality measures.
Conclusions: Despite the many factors that apparently go into the *U.S. News & World Report* rankings, reputation varies more widely than objective measures and is thus weighted more heavily in the final rankings.
Reviewer's Comments: With all of the publicly reported process measures currently available: pneumonia vaccination rates, smoking cessation counseling, beta-blocker for acute MI to name a few, it is a shame that the *U.S. News & World Report* rankings depend on reputation alone to measure the quality of hospital processes. Using reputation to create the rankings only fuels the high ranking of nationally renowned hospitals for the next year, failing to celebrate smaller, lesser known hospitals that may be excelling in providing high quality care. (Reviewer-Michelle Mourad, MD).

Keywords: Hospital Rankings, Quality Improvement

Print Tag: Refer to original journal article

Does a New Drug Offer New Hope for Atrial Fibrillation?

A Short-Term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients With Persistent Atrial Fibrillation: The DIONYSOS Study.

Le Heuzey J-Y, De Ferrari GM, et al:

J Cardiovasc Electrophysiol 2010; 21 (June): 597-605

Dronedarone is less effective than amiodarone but has less serious risks.

Background: Amiodarone remains the "gold standard" for anti-arrhythmic medical treatment of atrial fibrillation (AF) although efficacy is modest and significant serious adverse events abound. Dronedarone is a newer agent, pharmacologically similar to amiodarone but lacking the iodine moiety, found to have a shorter half-life with suspected decreased adverse event profile. Previously published trials have demonstrated that dronedarone has superior efficacy in controlling AF than placebo.
Objective: To compare dronedarone to amiodarone in efficacy and adverse events in the treatment of persistent AF.
Design: Multicenter, randomized double-blind study.
Participants: 504 patients with AF for ≥72 hours in whom anticoagulation with cardioversion and anti-arrhythmic medication therapy were planned.
Methods: Patients with previous amiodarone treatment, thyroid disease, prolonged QTc, paroxysmal AF, atrial flutter, severe heart failure, bradycardia, or high-grade AV block were excluded. Patients were initiated on amiodarone or dronedarone and electrically cardioverted 1.5 to 4.0 weeks later. Patients were followed by visit and ECG periodically through ≥6 months of follow-up. Composite primary end point was time to first AF recurrence or premature drug discontinuation.
Results: Patients were randomized 1:1 to the 2 groups. Mean age was 64 years with 20% aged >75 years with a median follow-up of 7 months. Primary end point occurred significantly less in patients receiving amiodarone (75.1% vs 58.8%) at 12 months. The drug was discontinued similarly in both groups (amiodarone 13.3% vs dronedarone 10.4%). The dronedarone group also had a higher rate of unsuccessful cardioversion. There was no significant difference in adverse events between groups although analysis with exclusion of gastrointestinal (GI) events demonstrated an improved safety profile with dronedarone. The dronedarone group had a lower incidence of supratherapeutic international normalized ratio with less hemorrhagic events than the amiodarone group.
Conclusions: Dronedarone was less effective than amiodarone in maintaining sinus rhythm and fostering cardioversion. Overall discontinuation rate is similar to amiodarone with a similar rate of side effects.
Reviewer's Comments: This short, but much needed trial showed that amiodarone remains the "gold standard" of drug treatment for AF. Unfortunately its success in maintaining sinus rhythm without side effects is abysmal. After excluding GI side effects, primarily diarrhea, dronedarone had a better side-effect profile. If this trial had persisted longer, likely more patients in the study would have discontinued amiodarone leading to a better outcome for the dronedarone group. Currently no drug exists that "cures" AF and a study involving first recurrence of AF seems destined to fail. Perhaps more practical patient-oriented end points such as reduction in total AF events, stroke, or hospitalization may be more appropriate. (Reviewer-Sumeet K. Mainigi, MD).

Keywords: Dronedarone, Anti-Arrhythmic Medications, Amiodarone, Atrial Fibrillation

Print Tag: Refer to original journal article

NAFLD Most Common Underlying Etiology of Cryptogenic Cirrhosis

Liver Transplantation of Patients With Cryptogenic Cirrhosis: Clinical Characteristics and Outcome.

Marmur J, Bergquist A, Stål P:

Scand J Gastroenterol 2010; 45 (January): 60-69

Weight loss in a patient with cryptogenic cirrhosis suggests decompensation of their liver disease.

Background: The frequency of underlying factors such as non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and denied alcohol abuse in the etiology of cryptogenic cirrhosis have not been clearly defined. Previous studies have found different rates of survival for patients with cryptogenic cirrhosis who undergo orthotropic liver transplantation (OLT).
Objective: To determine the presence of NAFLD in a group of patients with cryptogenic cirrhosis who were being evaluated for OLT and to compare the severity of liver disease and patient survival in OLT candidates with cryptogenic cirrhosis and those with cirrhosis of other etiologies.
Methods: Between 1990 and 2004, 470 adult patients with end-stage liver disease were evaluated for OLT. Of this group, 39 were found to have cryptogenic cirrhosis. Previously obtained histological and laboratory data were carefully reviewed for the purposes of this study.
Results: 17 (44%) patients diagnosed with cryptogenic cirrhosis were found to have NAFLD in a previous biopsy and/or clinical features of the metabolic syndrome. Two patients were found to have occult alcohol abuse and 1 had burnt out autoimmune hepatitis. Patients with cryptogenic cirrhosis had significantly higher frequencies of diabetes, ascites, hyponatremia, and weight loss. Patients with cryptogenic cirrhosis had similar survival to patients with cirrhosis of known etiology.
Conclusions: An underlying etiology was found in 51% of patients with cryptogenic cirrhosis who were being considered for OLT by re-evaluation of previously collected data. NAFLD was by far the most commonly discovered underlying etiology being found in 44% of cases. Despite the fact that patients with cryptogenic cirrhosis had more advanced liver disease at the time of OLT, their survival was similar to patients with other etiologies of cirrhosis. Weight loss was seen with increased frequency in cryptogenic cirrhosis suggesting it is a sign of liver decompensation and indicating a more urgent need for OLT evaluation.
Reviewer's Comments: As we are experiencing a worldwide epidemic of obesity and an ever greater incidence of the metabolic syndrome we can expect to be faced with an increased population of patients whose cirrhosis is caused not by viruses or alcohol abuse but by fatty livers. Although these trends are worrisome, it is good to know that when faced with a patient with end-stage liver disease caused by NAFLD that we can expect a good outcome if they need a liver transplant. (Reviewer-Michael M. Phillips, MD).

Keywords: Cryptogenic Cirrhosis, Non-Alcoholic Fatty Liver Disease

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Low Cancer Risk After Negative Colonoscopy Supports Longer Screening Intervals

Low Risk of Colorectal Cancer and Advanced Adenomas More Than 10 Years After Negative Colonoscopy.

Brenner H, Haug U, et al:

Gastroenterology 2010; 138 (March): 870-876

The low risk of colorectal cancer and advanced adenomas after a negative colonoscopy supports suggestions that screening intervals be extended to ≥10 years.

Background: It is currently unknown how often individuals who have had a negative screening colonoscopy should undergo a repeat examination.
Objective: To compare individuals undergoing screening colonoscopy who had at least 1 negative colonoscopy in the past to individuals who had never had a prior procedure.
Design: Retrospective observational study.
Participants: Patients who had elected to undergo screening colonoscopy and who had histories of negative colonoscopies in the past or who had never had colonoscopy before.
Methods: Patients who had chosen to have a screening colonoscopy filled out questionnaires asking whether or not they had had a prior colonoscopy. If they had, they were asked if polyps had ever been detected and the date(s) of any prior colonoscopies. Patients who had had at least 1 negative colonoscopy (self-reported) and no previous positive one were identified, as were those who had never had a colonoscopy before. The results of the current colonoscopy were used as the end point, and prevalences of both colorectal cancer and advanced adenoma were compared in the 2 groups. Patients with inflammatory bowel disease, a history of a colonoscopy within the past year, or those with missing information were excluded.
Results: 5181 subjects were recruited, but only 3234 met all eligibility criteria; 533 had had 1 or more previous negative colonoscopies. Almost half of that group had had the negative colonoscopy >10 years previously. The group with prior colonoscopies were somewhat older, more likely to be female, to have a family history of colorectal cancer, and to not have a smoking history. No cancers were detected in any of these 533 subjects; 41 cancers were found in the remaining 2701. Advanced adenomas were also less likely to be found in those with prior negative colonoscopies (25 vs 267). No relationship was found between the date of the prior colonoscopy and presence of an advanced adenoma. The risk reduction for advanced neoplasia was found only in the distal colon.
Conclusions: Since individuals who had had negative colonoscopies appeared to have only a very low risk of subsequent important neoplasia, the screening interval should be at least 10 years. The investigators noted that the phenomenon reflected a decreased likelihood for these individuals to develop neoplasia.
Reviewer's Comments: These data are difficult to interpret because of a potential selection bias. Individuals who had had a negative colonoscopy years earlier but then developed a lesion were excluded from this trial. Thus, the data apply only to people who have a negative examination and are unaware of any colonic problems many years later. Such individuals cannot be identified prospectively. (Reviewer-Ronald L. Koretz, MD).

Keywords: Colon Cancer Screening, Interval

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ACEI Plus Second Agent for Hypertension -- Amlodipine or Hydrochlorothiazide?

Cardiovascular Events During Differing Hypertension Therapies in Patients With Diabetes.

Weber MA, Bakris GL, et al:

J Am Coll Cardiol 2010; 56 (June 29): 77-85

In combination with an ACE inhibitor, the use of amlodipine is superior to hydrochlorothiazide in preventing cardiovascular events in diabetics with hypertension.

Background: Many patients with hypertension need more than one drug to control their blood pressure. Angiotensin-converting enzyme inhibitors (ACEIs) are commonly used. The most commonly added drugs to ACEIs are thiazide diuretics. This combination is effective at controlling blood pressure and is an inexpensive option. The Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial was performed to compare an ACEI (benazepril) with hydrochlorothiazide with a benazepril/amlodipine combination.
Objective: To evaluate data from the ACCOMPLISH trial, specifically the subgroup of diabetic patients.
Methods: A prespecified analysis of the ACCOMPLISH trial was an analysis of outcomes in diabetic patients. A total of 6946 patients with diabetes and hypertension were randomized to receive benazepril plus hydrochlorothiazide or benazepril plus amlodipine. The primary end point was a composite of vascular complications (cardiovascular death, hospitalization for angina, resuscitated cardiac arrest, myocardial infarction, cardiac revascularization, and stroke).
Results: The mean blood pressures were not significantly different (131.5/72.6 mm Hg for those receiving benazepril/amlodipine and 132.7/73.7 mm Hg for those receiving benazepril/hydrochlorothiazide). Primary end points were fewer in patients who received amlodipine, 8.8% versus 11% for those receiving hydrochlorothiazide (HR, 0.79; CI, 0.68 to 0.92; *P* =0.003). In a subgroup of diabetic patients at very high risk, there were even more significant differences, 13.6% for those treated with an amlodipine regimen versus 17.3% on the diuretic regimen (HR, 0.77; *P* =0.007).
Conclusions: The combination of benazepril/amlodipine was better in reducing cardiovascular end points than benazepril/hydrochlorothiazide in diabetic patients.
Reviewer's Comments: This study looks as if amlodipine combined with benazepril is better than the standard of combining it with hydrochlorothiazide. The results were significant, favoring amlodipine. I am concerned about what was measured, however. The primary end point was a composite of multiple cardiovascular outcomes, including hospitalization for angina. There was no significant difference between the regimens in fatal and non-fatal myocardial infarction, hospitalization for unstable angina, stroke, cardiovascular death, or all-cause death. Interestingly, there was a very significant (*P* <0.001) difference in renal outcomes, favoring the amlodipine group. The number needed to treat for the primary composite end point was 45. The group receiving amlodipine had significantly more side effects (one third of these patients had peripheral edema). (Reviewer-Douglas S. Paauw, MD).

Keywords: Hypertension, ACE Inhibitors, Diabetes

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Reducing BP With CPAP -- Nothing to Yawn About

Continuous Positive Airway Pressure Treatment in Sleep Apnea Patients With Resistant Hypertension: A Randomized, Controlled Trial.

Lozano L, Tovar JL, et al:

J Hypertens 2010; 28 (June 23): epub ahead of print

In patients requiring 3 to 5 antihypertensive medications, evaluation for obstructive sleep apnea and subsequent treatment with CPAP therapy may help reduce 24-hour blood pressure and restore nocturnal dipping.

Background: One third of U.S. adults have hypertension, which is inadequately controlled in approximately 50%. Obstructive sleep apnea (OSA) is associated with hypertension (and other cardiovascular disease). Continuous positive airway pressure (CPAP) has shown a small effect in reducing blood pressure in people with severe OSA but has little to no effect in those with milder OSA.
Objective: To examine the effect of CPAP therapy in people with resistant hypertension and OSA.
Participants/Methods: The study involved hypertension clinic patients taking 3 to 5 antihypertensive medications but with elevated blood pressures (>140/90 mm Hg in clinic or >125/80 mm Hg on 24-hour monitoring; n=96). Patients had an apnea-hypopnea index >15 on polysomnography (n=75) and were randomized to either CPAP therapy or to usual treatment for 3 months; 24-hour ambulatory blood pressure monitoring was performed at the start and end of the study.
Results: 64 patients completed the study (9 in the CPAP arm either refused to try CPAP or were unable to tolerate it; 2 were lost in the usual treatment arm). Median CPAP use was 5.8 hours a night. After 3 months, those with 24-hour resistant hypertension (rather than in-clinic elevated readings only) who used CPAP for >5.8 hours/night showed a reduction in 24-hour systolic (-9.7 mm Hg) and diastolic (-7.0 mm Hg) blood pressures and in daytime diastolic blood pressure (-6.1 mm Hg). Nocturnal dipping of blood pressure was present in 50% of the CPAP group at baseline and in 76% at study end; there was no change in the usual treatment arm.
Conclusions: In patients with resistant hypertension and OSA who are able to tolerate nocturnal CPAP therapy, treatment for >5.8 hours a night for 3 months reduces 24-hour systolic and diastolic blood pressures and daytime diastolic blood pressure. It also restores nocturnal dipping in half of nondippers.
Reviewer's Comments: Seventy-eight percent of these patients on 3 to 5 blood pressure medications had OSA (similar to at least one prior study), and 76% of those randomized to CPAP were able to use it. Half the patients used CPAP for >5.8 hours a night (the group's median use and the level above which a statistically significant benefit was seen). Therefore, perhaps up to 30% of patients with resistant hypertension could potentially benefit (blood pressure wise) from evaluation and treatment for OSA. The absolute decrease in daytime blood pressure with nocturnal CPAP is modest, but restoration of normal dipping during sleep and a mean decrease in blood pressure over 24 hours by almost 10 mm Hg systolic and 7 mm Hg diastolic are nothing to yawn about. (Reviewer-Eliza L. Sutton, MD).

Keywords: Hypertension, Obstructive Sleep Apnea, Continuous Positive Airway Pressure

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Is an LDL of Less Than 70 Enough?

Clinical Predictors of Plaque Progression Despite Very Low Levels of Low-Density Lipoprotein Cholesterol.

Bayturan O, Kapadia S, et al:

J Am Coll Cardiol 2010; 55 (June 15): 2736-2742

More than 20% of patients with LDL ≤70 mg/dL have disease progression assessed by intravascular ultrasound.

Background: The benefits of aggressive lipid-lowering therapy in preventing cardiovascular events are well demonstrated, and data demonstrate regression of plaque in patients achieving very low LDL-C levels with medical therapy. However, despite achieving an LDL ≤70 mg/dL, some patients nonetheless have progression of atherosclerotic coronary disease as evaluated by intravascular ultrasound (IVUS).
Objective: To evaluate the risk factors for progression of plaque burden in patients with treated LDL ≤70 mg/dL.
Methods: The authors used data from 7 trials of atherosclerosis progression/regression that utilized IVUS. Multiple medical therapies were used in these trials, but all patients must have had coronary disease (>20% stenosis of at least one epicardial coronary artery) as seen on a diagnostic angiogram performed for clinical reasons to enter in the respective trials. Those with on-treatment LDL ≤70 mg/dL were classified as either progressors (>5% increase in atheroma volume) or nonprogressors. IVUS measurements were done in a standard fashion.
Results: 951 patients were included, with 200 classified as progressors. There were no baseline differences in age, gender, clinical diagnoses, or medication use between groups. Mean follow-up was 654 days in progressors and 674 days in nonprogressors. Independent predictors of plaque progression during follow-up included baseline burden of disease (those with greater plaque volumes were more likely to progress), diabetes mellitus, a greater increase in systolic blood pressure, a smaller increase in HDL, and a smaller decrease in apoB levels. C-reactive protein and LDL-C were not associated with progression. There was no difference in a composite end point of death, myocardial infarction, or stroke between the progressors and nonprogressors (1.8% and 1.9%).
Conclusions: Residual risk factors are associated with plaque progression, and plaque progression occurs in >20% of patients with coronary artery disease (CAD) and LDL ≤70 mg/dL. The finding that apoB levels were associated with plaque progression suggests that particle size may be important.
Reviewer's Comments: For 2 reasons, this study is largely hypothesis generating rather than involving data that can be used to change practice. Progression as assessed by IVUS does not always directly translate to clinical differences and often serves as a surrogate end point. Additionally, while the differences between groups are statistically significant, they were not practically different. For example, the change in HDL levels at follow-up between nonprogressors and progressors was 4.9 and 5.4, respectively, with actual levels at follow-up of 49.9 and 50.7, respectively. However, the identification that >20% of patients with optimal LDL levels had disease progression and the associated risk factors emphasizes the multifactorial nature of CAD progression and the need for more data to refine our treatments. (Reviewer-Karen Stout, MD).

Keywords: Coronary Disease, Risk Factors

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