Contrary to popular belief, evidence that intensive glucose-lowering therapy improves macrovascular outcomes in patients with type 2 diabetes is limited. In two new randomized trials, researchers address this issue.

The NIH-sponsored ACCORD study involved 10,251 type 2 diabetic patients (mean age, 62; median glycosylated hemoglobin [HbA₁c], 8.1%) with known cardiovascular disease or at least two additional risk factors. Patients received either intensive therapy (target HbA₁c, 6%, with antidiabetic regimens individualized by clinicians) or standard therapy (target HbA₁c, 7%–7.9%). Although glycemic control was significantly better with intensive treatment than with standard treatment throughout the trial (median HbA₁c, 6.4% vs. 7.5%), the trial was stopped after an average follow-up of 3.5 years, because mortality was higher in the intensive-treatment group than in the standard-treatment group (5% vs. 4%; P=0.04). Moreover, the groups did not differ significantly in the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (6.9% vs. 7.2%). Severe hypoglycemia and weight gain were more common in the intensive-treatment group, but the factors mediating the higher mortality with intensive treatment were unclear.

The second study — the ADVANCE trial — involved 11,140 patients (mean age, 66; median HbA₁c, 7.2%). The intensively treated group received the sulfonylurea glipizide as initial therapy (with other drugs added as required to reach target HbA₁c of 6.5%), and the standard-treatment group received any drugs except glipizide (with no specified target HbA₁c). Although HbA₁c averaged 6.5% with intensive treatment and 7.3% with standard treatment during 5 years of follow-up, no significant difference was noted between groups for the primary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (10.0% vs. 10.6%) or for all-cause mortality. The microvascular outcome of new or worsening nephropathy occurred significantly less often in the intensive-treatment group (4.1% vs. 5.2%), but severe hypoglycemia was more common with intensive treatment. This study was supported by the maker of glipizide.

**Comment:**

Yet again, presumably favorable modification of a surrogate endpoint — in this case, HbA₁c — did not necessarily improve clinical outcomes in high-risk populations. Why intensive treatment was associated with increased mortality in ACCORD but not in ADVANCE is unclear, the trials are consistent in showing no significant effect of tight glycemic control on macrovascular events. Clinicians should aim for reasonable glycemic control in older diabetic patients, but aggressive attempts to normalize HbA₁c are not routinely warranted in this patient population.

— Allan S. Brett, MD


**More Olive Oil, Please: Mediterranean Diet and Type 2 Diabetes Prevention**

A Mediterranean diet — which includes high intake of fiber and monounsaturated fatty acids derived from vegetable fat (especially olive oil), low intake of saturated fatty acids, and moderate alcohol intake — lowers risk
for nonfatal myocardial infarction and for death due to coronary heart disease. Limited evidence suggests that this diet also can prevent type 2 diabetes. To further investigate this issue, Spanish researchers conducted a prospective cohort study that involved more than 13,000 university graduates without diabetes at baseline. Dietary habits were tracked using validated food-frequency questionnaires; participants were classified as having low, moderate, or high adherence to a Mediterranean diet.

Thirty-three participants developed type 2 diabetes during a median follow-up of 4.4 years. Compared with low dietary adherence, high adherence was associated with an 83% lower risk for developing diabetes, and moderate adherence was associated with a 60% lower risk (adjusted for various demographic, lifestyle, and clinical variables). Both results were statistically significant.

**Comment:**
A Mediterranean diet improves glycemic control and lipid profiles; therefore, this type of diet likely lowers risk for developing type 2 diabetes by improving insulin sensitivity. Furthermore, as the authors point out, a Mediterranean diet is highly palatable and should appeal to patients and clinicians alike. — **Paul S. Mueller, MD, MPH, FACP**


### Aliskiren to Reduce Proteinuria in Diabetic Nephropathy

Aliskiren (Tekturna), a direct renin inhibitor, was FDA-approved in 2007 for treatment of hypertension. Researchers conducted this industry-sponsored randomized trial to determine whether dual blockade of the renin-angiotensin-aldosterone system — with the combination of aliskiren and the angiotensin-receptor blocker losartan — reduces proteinuria in patients with diabetic nephropathy. The trial involved 599 patients with type 2 diabetes, hypertension, and nephropathy (urinary albumin-to-creatinine ratio between 300 and 3500 mg/g). Patients with glomerular filtration rate (GFR) <30 mL/min or serum potassium >5.1 mEq/L were excluded.

Patients received either losartan plus aliskiren or losartan plus placebo. At 6 months, the mean urinary albumin-to-creatinine ratio was significantly reduced by 20% in the aliskiren group, compared with the placebo group. Mean blood pressure was significantly lower with aliskiren than with placebo, but only by 2 mm Hg (systolic) and 1 mm (diastolic). GFR did not differ significantly between the groups.

**Comment:**
This trial demonstrates that aliskiren in combination with an angiotensin-receptor blocker has a moderate additive effect in reducing proteinuria in patients with diabetic nephropathy. However, the study's duration was too short to examine clinical endpoints (e.g., progression to advanced or end-stage renal disease) or to ensure long-term safety. Thus, use of aliskiren solely to reduce proteinuria seems premature at this time. — ***Allan S. Brett, MD***


### Inequitable Access to Coronary Angiography Linked with Higher Rates of Coronary Events and Death

Many studies have shown that ethnic minorities, women, elders, and the poor have less access to others to effective interventions for stable angina and acute coronary syndromes. Does reduced access lead to worse cardiac outcomes? In a 5-year multicenter cohort study, investigators reviewed medical records of 10,634 patients with recent onset angina who visited “rapid access chest pain clinics” in the U.K.

An independent panel determined that 1375 patients were appropriate candidates for coronary angiography. Of these, only 420 patients (31%) underwent the procedure. In multivariate analysis, coronary angiography was significantly less likely to be performed in patients aged 65 and older (compared with patients younger than 50), in women (compared with men), in patients of southern Asian ethnicity (compared with white patients), and in patients in the economically poorest quintile (compared with patients in other economic quintiles). In all subgroups, patients who did not undergo coronary angiography had higher rates...

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Osteoporosis Screening in Men

The American College of Physicians (ACP) has issued a clinical practice guideline on screening for osteoporosis in men. The guideline is based on a systematic evidence review of 269 studies that examined risk factors and 20 that examined diagnostic tests. Although often viewed as a problem primarily of women, osteoporosis is prevalent among U.S. men (affecting 7% of white men), underdiagnosed, and often untreated.

The review identified moderate- to high-quality evidence that the following risk factors are associated with low bone-mineral density (BMD) and osteoporotic fractures in men:

- Age, >70
- Low body weight
- Weight loss
- Physical inactivity
- Previous osteoporotic fracture
- Prolonged systemic corticosteroid therapy or androgen deprivation therapy

Other identified risk factors with low-to-moderate quality evidence were smoking, spinal cord injury, and alcohol use.

The ACP recommends periodic assessment of risk factors in older men and screening with dual energy x-ray absorptiometry (DXA) for men who are at increased risk and are candidates for drug therapy.

**Comment:**

This recommendation is based on evidence that is limited primarily by the study’s focus on BMD and not fractures. I am surprised by the recommendation for screening because the review did not include studies that evaluated treatments to reduce fracture risk among men with risk factors who were identified as having osteoporosis when screened by DXA. In its recommendations for screening of women, the U.S. Preventive Services Task Force provided evidence of treatment benefit in asymptomatic women; the task force has not issued a guideline that addresses men, but I would be interested in its “take” on this topic.

— Richard Saitz, MD, MPH, FACP, FASAM


Early Repolarization in Survivors of Idiopathic Ventricular Fibrillation

Early repolarization is a common electrocardiographic finding that is thought to be benign. However, experimental evidence suggests that early repolarization is potentially associated with sudden cardiac arrest. In an international retrospective study of data from 22 tertiary-care arrhythmia centers, investigators compared 206 survivors of idiopathic ventricular fibrillation (VF) with 412 age-, sex-, and race-matched controls. Idiopathic VF was defined as sudden cardiac arrest occurring in the absence of present or inducible structural or electrical abnormalities, including (among others) long QT syndrome, short QT interval, and Brugada syndrome.

Early repolarization was present in 64 case subjects (31%) versus 21 control subjects (5%, P<0.001) and, when present, was also greater in magnitude in case subjects than in control subjects (J-point elevation, 2.0±0.9 mm vs. 1.2±0.4 mm; P<0.001). Predictors of early repolarization included male sex and occurrence of arrhythmias during sleep.

All case subjects with idiopathic VF received an implantable cardioverter-defibrillator. During a mean follow-up of 61 months, idiopathic-VF patients with early repolarization were significantly more likely than those without early repolarization to have recurrent VF.

**Comment:**

Repolarization abnormalities underlie most instances of ventricular fibrillation both in patients with and in those without structural heart disease. Findings from large clinical series indicate that early repolarization is a benign condition. Yet the current results suggest that in some individuals, early repolarization is a manifestation of a primary electrical disease. How to pick these needles out of the haystack is not yet clear, so these findings should not prompt a change in the care of patients with early repolarization. — Mark S. Link, MD

Dr. Link is an Associate Professor of Medicine at New England Medical Center and Tufts University School of Medicine, Boston.


Nesiritide Has No Role for Acute Decompensated Heart Failure in the ED

Nesiritide, a drug that is structurally similar to naturally occurring B-type natriuretic peptide, initially was thought to increase diuresis and decrease morbidity and length of stay in patients with acute decompensated heart failure (ADHF). But nesiritide has fallen out of favor because it is expensive, has been linked to increased rates of renal failure, and has been shown to have no advantages over conventional therapy.

In a manufacturer-funded, randomized, placebo-controlled trial, investigators evaluated the effect of adding an 8-hour nesiritide infusion (2 μg/kg bolus followed by 0.01 μg/kg/min) to conventional therapy in patients who presented to an urban ED with ADHF. Of 101 patients with acute decompensated heart failure (ADHF), 88% of those who identified themselves as “African Americans” (but in only about 2% of those who identified themselves as “European Americans”) and that acts as a genetic β-blocker. A prospective study of 375 black patients with one or two copies of this polymorphism showed that they were protected against progressive heart failure as if they were taking β-blockers. Indeed, observational studies showed that β-blockers did not improve cardiac outcomes in patients with this polymorphism, even though such drugs provide marked protection to the 75% of blacks who do not carry the polymorphism. The polymorphism also protected mice against experimental catecholamine-induced cardiomyopathy and heart failure.

Comment:
The authors’ rationale for conducting this study was that despite compelling evidence against use of nesiritide in the ED for patients with acute decompensated heart failure, this treatment had not been studied in a population with a high proportion of black patients. Black patients could represent a different clinical scenario, and the drug could have had a role in this population. However, the findings show that this is not the case. At present, nesiritide has no role in the ED.

— Richard D. Zane, MD, FAAEM
Dr. Zane is Vice Chairman of the Department of Emergency Medicine at Brigham and Women’s Hospital and an Assistant Professor at Harvard Medical School, Boston.


Inherited Polymorphism Protects American Blacks from Progressive Heart Failure

In the 1970s, β-blockers were thought to be contraindicated in patients with heart failure, but today, they are a mainstay of therapy. Patients with heart failure have chronically elevated levels of norepinephrine, which attaches to β-adrenergic receptors on myocytes and stimulates a signaling cascade. Blocking this process protects myocytes from hypertrophy and cell death. A multi-institutional team has identified a common polymorphism in one molecule, GRK5, that is present in 25% of people who identified themselves as “African Americans” (but in only about 2% of those who identified themselves as “European Americans”) and that acts as a genetic β-blocker. A prospective study of 375 black patients with one or two copies of this polymorphism showed that they were protected against progressive heart failure as if they were taking β-blockers. Indeed, observational studies showed that β-blockers did not improve cardiac outcomes in patients with this polymorphism, even though such drugs provide marked protection to the 75% of blacks who do not carry the polymorphism. The polymorphism also protected mice against experimental catecholamine-induced cardiomyopathy and heart failure.

Comment:
If this finding is confirmed, we someday could employ a genetic test for this polymorphism before deciding whether to recommend β-blockers to black patients with, or at risk for, heart failure. This discovery could also lead to new insights about the biology of heart failure and new therapies based on that knowledge.

— Anthony L. Komaroff, MD

Delay to Hospital Presentation Among Patients with STEMI

Time from symptom onset to presentation affects the extent of myocardial damage and potential treatment options for patients with ST-segment-elevation myocardial infarction (STEMI). Investigators used data from a national registry to study temporal trends and risk factors for delays in presentation. Nearly 500,000 patients with STEMI were included in the analysis; 67% were men, and 86% were white. Mean times from symptom onset to hospital presentation decreased from 123 minutes in 1995 to 113 minutes in 2004. White men had the shortest times to presentation. Female sex, older age, black race, Latino ethnicity, presence of diabetes, and lack of commercial insurance all predicted longer times to presentation. For example, older black women (age, >70) with diabetes presented, on average, more than 60 minutes later than did younger white men without diabetes.

Comment:
In this observational study, patient characteristics and insurance status were associated with longer times from symptom onset to presentation for STEMI. Even patients with previous MIs had delays that averaged approximately 115 minutes. These findings highlight the need to broaden our educational efforts for our patients and the general public to shorten presentation delays.

— Jamaluddin Moloo, MD, MPH

Poor Adherence to Once-Daily Antihypertensive Drugs Is Common

Poor adherence to antihypertensive drug treatment is a major reason for insufficient blood pressure control. In this longitudinal study, investigators used data from 21 clinical studies to determine adherence among 4783 patients who were prescribed 1 of 43 once-daily antihypertensive drugs. Adherence was determined using medication containers that electronically record the date and time of each opening. At 1 year, almost half the patients had stopped treatment altogether (non-persistence). On any given day, about 10% of scheduled doses were missed (nonexecution). Overall, 95% of patients missed a single dose at least once yearly, half missed a single dose once monthly, and nearly half took drug holidays lasting longer than 3 days at least once yearly. Failure to execute was significantly more common between April and September and on weekends. Morning takers were significantly more likely to execute than evening takers. Patients with better execution were significantly more likely to persist taking the drug.

Estimated adherence was determined using medication containers that electronically record the date and time of each opening. At 1 year, almost half the patients had stopped treatment altogether (non-persistence). On any given day, about 10% of scheduled doses were missed (nonexecution). Overall, 95% of patients missed a single dose at least once yearly, half missed a single dose once monthly, and nearly half took drug holidays lasting longer than 3 days at least once yearly. Failure to execute was significantly more common between April and September and on weekends. Morning takers were significantly more likely to execute than evening takers. Patients with better execution were significantly more likely to persist taking the drug.
Comment:
As the authors conclude, patients at risk for quitting medication need reinforcement to continue (unless the reason for quitting is an adverse effect of the drug), whereas those who execute poorly need help integrating dosing into their daily routines. These findings also suggest that medications should be taken in the morning and that barriers to execution during vacations and weekends should be addressed. Finally, these results suggest that, in patients with insufficiently controlled blood pressure, clinicians should first inquire about and address nonadherence before adding another drug to the patient’s regimen, which would make adherence only more difficult.
— Paul S. Mueller, MD, MPH, FACP


Particulate Air Pollution and DVT Risk

Particulate air pollution is associated with excess risks for heart disease and stroke. In a case-control study, conducted in northern Italy, researchers assessed whether such pollution also might be linked to venous thrombosis. A total of 871 patients who were diagnosed between 1995 and 2005 with lower-limb deep venous thrombosis (DVT) and 1210 healthy controls were enrolled in the investigation. The researchers estimated participants’ exposure to particulate-matter air pollutants <10 µm in diameter (PM₁₀) during the year before DVT diagnosis (cases) or examination (controls), based on monitored levels of PM₁₀ in nine geographic regions.

Mean PM₁₀ exposure during the year before diagnosis or examination varied by region, ranging from 12 to 52 µg/m³. After controlling for multiple factors including age, sex, use of oral contraceptives, and factor V Leiden or prothrombin mutation, investigators found that, for each 10-µg/m³ increase in PM₁₀ exposure, DVT risk rose by 70%.

Comment:
These findings suggest that exposure to high concentrations of particulate-matter air pollutants correlates with heightened risk for DVT. The association, if confirmed, introduces a novel risk factor for development of DVT and extends the known prothrombotic effect of particulate air pollution (potentially secondary to high plasma levels of coagulation proteins) from the arteries to the veins.
— Jamaluddin Moloo, MD, MPH

Timely Preop Antibiotics Should Reduce Wound Infections — Shouldn’t They?

Antibiotics given within a small preoperative window reduce postoperative wound infection rates in both animal and human studies. The data are solid that adherence to this standard of care has become one of the performance measures by which hospitals are publicly rated. But how does it all sort out in real life?

Retrospective data from 9195 elective surgical procedures that were performed in almost 100 Veterans Affairs hospitals were analyzed to correlate the timely administration of antibiotics with wound infection rates. Overall, 86.4% of patients received antibiotics within the designated 1-hour window before skin incision (or within 2 hours for vancomycin and the quinolones); 4.7% of patients developed wound infections, with slightly, although not significantly, more infections in those who did not receive timely antibiotics.

However, many variables were associated with both failure to receive timely antibiotics and development of wound infections, including American Society of Anesthesiologists class 3 or 4, low serum albumin levels, a clean-contaminated wound (entry into the respiratory, gastrointestinal, or genitourinary tracts without significant spillage), longer operative time, and inpatient status. In a multivariate analysis, timely antibiotic administration offered no significant protection against wound infection — in fact, in vascular operations, it was associated with a slightly higher rate of wound infections.

Comment:
You might have seen the ads that ran in newspapers across the nation several weeks ago that informed readers about how their local hospitals scored on this particular benchmark of quality medical care. But this thought-provoking study encapsulates the peril involved in assuming that the conclusions of a clinical study will hold true in real life — let alone remain durable enough to be established as a public marker of quality. The authors suggest that, whereas the data that support the efficacy of preop antibiotics are sound, the 1-hour window could be unnecessarily tight and not a good marker for distinguishing “good” hospitals from “bad” ones. In fact, the waters have been muddied further by another recent study in which antibiotic dosing that occurred less than 30 minutes before skin incision was associated with a higher incidence of surgical site infection than was dosing that occurred 30 to 60 minutes before incision (Ann Surg 2008; 247:918).
— Abigail Zuger, MD


UTIs, Vesicoureteral Reflux, and Antibiotic Prophylaxis

Vesicoureteral reflux (VUR) is a common finding in children with urinary tract infections (UTIs). Early detection followed by antibiotic prophylaxis might reduce renal scarring, which is thought to lead to impaired renal.
function. This multisite trial involved 218 children (age range, 3 months to 18 years) with acute pyelonephritis; 113 had grade I–III VUR, and 105 had no VUR. Patients were randomized to receive either daily urinary antibiotic prophylaxis (trimethoprim-sulfamethoxazole or nitrofurantoin for 1 year) or no prophylaxis.

After 1 year, VUR resolution rates were similar for patients who did or did not receive prophylaxis. Among patients with VUR, recurrent UTI rate was similar for those who did or did not receive prophylaxis (20% and 24%). Among patients without VUR, the difference in recurrence rate between those who did or did not receive prophylaxis approached statistical significance (9% and 24%). Rates of renal scarring, detected by renal scintigraphy, were similar for patients who did or did not receive prophylaxis (9% and 3% for those with VUR, and 5% and 7% for those without VUR).

**Comment:**

These results — antibiotic prophylaxis for children with mild-to-moderate VUR did not prevent recurrent UTI or the development of renal scars — call into question the conventional wisdom of antibiotic prophylaxis for VUR. An editorialist suggests that, in order to prevent UTI, prophylaxis might require more creativity and involve changing antibiotics every 2 to 4 weeks. However, she also concludes that prophylaxis for patients with low-grade VUR does not appear to be beneficial.

— Howard Bauchner, MD


**St. John’s Wort in ADHD**

St. John’s wort (Hypericum perforatum) is one of the most common herbal treatments given to children with attention-deficit/hyperactivity disorder (ADHD). Like atomoxetine (Strattera) — which is approved for use in children with ADHD — St. John’s wort is a norepinephrine reuptake inhibitor.

In a clinical trial conducted at a college of naturopathic medicine, 54 children and adolescents who met DSM-IV criteria for ADHD (age range, 6–17 years; mean age, 10) were randomized to thrice-daily St. John’s wort (300 mg) or placebo for 8 weeks after a 1-week placebo run-in. Nearly half the children previously had taken medications for ADHD. Based on blinded clinical evaluations and standardized assessments at 1, 2, 4, 6, and 8 weeks, no difference was observed in mean clinical improvement or in the proportion of children who met criteria for clinically significant improvement, on both intent-to-treat and per-protocol analyses. In addition, the number of adverse events did not differ between groups.

**Comment:**

This study, purported to be the first placebo-controlled trial of St. John’s wort in children and adolescents, showed no benefit in ADHD. The study also is a good example of the type of rigorous research needed to assess many unstudied remedies, both “conventional” and “complementary.”

— Thomas L. Schuenke, MD


**Attempted Suicides in Anorexia Nervosa**

Suicide is the second leading cause of death in anorexia nervosa (AN), and the suicide rate is eight times higher among young women with AN than in young women generally. To better delineate the issue, investigators analyzed data from 413 participants with current or lifetime AN (95% female) who were enrolled in an NIMH genetics study.

Overall, 17% had made a suicide attempt. An attempt was significantly more common among those with binge-eating, purging, or both (21%–29%) than among those with the restrictor subtype (7%).

Of all suicide attempters, 52% reported one attempt; 39% reported two to four attempts; and 9% reported five or more attempts. Impulsivity accounted for 49% of attempts, with the remainder somewhat or thoroughly premeditated (each, 25%). Seventeen percent reported concurrent alcohol abuse at the time of the worst or only attempt, 9% reported concurrent drug abuse, and 82% reported a concurrent depressive episode.

**Comment:**

Since this study recruited from both clinical and nonclinical populations, the very high rates of severe suicidality in patients with AN, particularly of the binge-eating/purging subtype, are particularly alarming. Clinical studies of AN patients have reported even higher rates. Clinicians assessing and treating these patients should be alert to the constant risk for suicide, particularly among patients with indications of impulsivity and the other comorbid conditions identified here.

— Joel Yager, MD

*Dr. Yager is a Professor and Vice Chair for Education and Academic Affairs in the Department of Psychiatry at the University of New Mexico School of Medicine.*

*Bulik CM et al. Suicide attempts in anorexia nervosa. Psychosom Med 2008 Apr; 70:378.*

**Contraceptive Use Among Women with Epilepsy**

Although approximately 1 million women in the U.S. have epilepsy, little is known about their use of contraceptives. To shed light on this issue, researchers conducted a cross-sectional study among 18- to 44-year-old English- or Spanish-speaking women who presented for routine care at a New York City epilepsy center.

The 148 participants reported a total of 181 pregnancies, 50% of which had been unplanned. Unplanned pregnancies were significantly more common among women who described themselves as Spanish- rather than English-speaking, those on Medicaid, and those with low household incomes. Of the 78 women who reported having vaginal intercourse during the preceding month, only 58 (74%) were using contraception. Just 31 were using a highly effective method, including 2 who were using intrauterine devices (IUDs) or long-acting progesterin injections. Almost one third of the women who used hormonal contraceptives also took cytochrome P450 enzyme–inducing antiepileptic drugs, potentially increasing their susceptibility to pregnancy.

**Comment:**

Although these women had a chronic illness demanding careful pregnancy planning, their reproductive experiences were similar to those seen in healthy women of reproductive age. In my view, the minimal use of depot medroxyprogesterone acetate (known to have an
ameliorating effect on some forms of epilepsy) and of IUDs is disappointing. These findings suggest the need for more-careful attention to contraception and family planning among clinicians who care for women with epilepsy.

— Robert W. Rebar, MD


Terlipressin for Hepatorenal Syndrome

Terlipressin, a vasopressin analogue and a vasoconstrictor, has been used in Europe to treat patients with hepatorenal syndrome. The drug reverses the splanchnic vasodilation associated with cirrhosis and thus increases effective arterial volume and renal perfusion. Only a few dozen patients have been studied in controlled trials; these two new studies add considerably to the literature.

A randomized trial, conducted mostly in the U.S., involved 112 patients with type 1 HRS (associated with rapidly declining renal function) and a mean baseline creatinine level of 3.9 mg/dL. Patients received IV albumin plus terlipressin or albumin plus placebo for a maximum of 2 weeks. Treatment success (defined as serum creatinine level ≤ 1.5 mg/dL on 2 occasions at least 48 hours apart, without dialysis, death, or relapse at 14 days) occurred in 25% of terlipressin recipients and in 13% of placebo recipients (P = 0.09). When a less-stringent endpoint of HRS reversal (a single serum creatinine measurement ≤ 1.5 mg/dL) was used, improvement was statistically significant for terlipressin compared with placebo (34% vs. 13%; P = 0.01). However, survival at 6 months was about 40% in both groups.

In a similar randomized trial from Spain that involved 46 patients, a “complete response” (reduction in serum creatinine level to < 1.5 mg/dL during treatment) was more common among terlipressin recipients than among controls (39% vs. 4%), but survival at 3 months did not differ significantly between the two groups (27% vs. 19%). More cardiovascular adverse events were reported in the terlipressin groups than in the control groups in both studies.

**Comment:**
Terlipressin improved renal function, but not short-term mortality, in both studies. This outcome suggests that terlipressin’s primary role might be as a bridge to liver transplantation. Terlipressin is not FDA-approved in the U.S., where the combination of octreotide plus midodrine is often used to treat hepatorenal syndrome.

— Allan S. Brett, MD


Could Intensivist Management Actually Increase ICU Mortality?

Past studies (with substantial methodological limitations) have suggested that critical care physician (intensivist) management can lead to better clinical outcomes. To examine this hypothesis, researchers evaluated more than 100,000 patient records from 123 intensive care units at 100 hospitals. Critical care physicians were defined as those who were recognized as such by their institutions, whether or not they were board-certified or fellowship-trained in critical care; they had responsibility for overall patient management. In most units, the choice of whether to involve an intensivist was left to each patient’s admitting physician.

Patients who were managed by intensivists were more severely ill and underwent more procedures. In an effort to account for this source of confounding, mortality analyses were done separately for different levels of illness severity and included the likelihood that a patient would be cared for by an intensivist (based on a technique called a propensity scoring). Intensivist management was associated with higher mortality (odds ratios, 1.18 to 2.83). The largest effects on mortality occurred among the least severely ill patients.

**Comment:**
This study methodology is about as good as it could be with retrospective data. The findings are plausible and might be explained by differences in clinical practices (e.g., more procedures and their attendant complications). But editorialists (both practicing intensivists) note that the findings are in conflict with prior literature, and they express concern that open ICUs with elective intensivist consultation — rather than closed ICUs run by intensivists — were the source of much of these data. Hence, they call for replication of these findings and identification of a mechanism for the effect. I think there is a fair chance that the patients cared for by intensivists were sicker in ways that could not be accounted for in the analyses. In any case, this study should lead to a careful examination of assumptions about the best management approaches for critically ill patients.

— Richard Saitz, MD, MPH, FACP, FASAM


No Need to Select Specific Antihypertensive Drugs According to Age

Some authorities recommend selective use of antihypertensive drugs based on patient age. For example, some recommend angiotensin-converting enzyme inhibitors and β-blockers as initial blood-pressure-lowering drugs for younger patients and diuretics for older patients because younger patients tend to have higher renin levels than do older patients. However, little evidence supports this recommendation. In this meta-analysis of 31 prospective randomized trials that involved more than 190,000 patients, investigators compared relative risk reductions for cardiovascular events (stroke, coronary heart disease, and heart failure) associated with various antihypertensive drug regimens in younger (age, < 65) versus older (age, ≥ 65) adults.

In trials that compared antihypertensive regimens with placebo, or more-intensive antihypertensive regimens with less-intensive regimens, relative risk reductions did not differ significantly between the two age groups. Similar results were found for trials in which antihypertensive regimens based on different drug classes were compared. Finally, risk reduction achieved per unit of reduction in blood pressure reduction did not differ between the two age groups.

**Comment:**
Both younger and older adults with hypertension benefit from blood pres-
Settling the Controversy About Long-Acting β-Agonists?

In a 2006 meta-analysis that was conducted by investigators with no industry ties, use of long-acting β-agonists (LABAs) was associated with asthma-related death (JAMA 2006;295:1250-1257). A limitation of this study was that many patients who received LABAs were not also taking inhaled corticosteroids. Now, investigators report results of a study in which inhaled corticosteroids alone were compared with inhaled corticosteroids plus salmeterol for the treatment of asthma. Compared with corticosteroids alone, combination therapy was associated with:

A. fewer hospitalizations.
B. fewer severe exacerbations.
C. lower mortality.
D. higher mortality.

Category: Asthma
Exam Title: JW (General): Steroid Therapy, Disease Persistence, COPD
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This is one of four questions in a recent Journal Watch Online CME exam. Click on the CME link from the Journal Watch summary online at http://www.jwatch.org or go to http://cme.jwatch.org and view the exam listings. User name and password are required.

Comment:
Combining LABAs with inhaled corticosteroids does not appear to increase risk for serious adverse events. Combination therapy is also associated with fewer severe exacerbations and relief of symptoms. An editorialist notes that the studies included in this meta-analysis were designed as efficacy studies (and, therefore, were not powered to detect rare adverse events) and reflect ideal rather than real-world practices. He recommends reserving LABA-corticosteroid combinations for patients whose asthma is not controlled adequately by inhaled steroids alone, and only for patients who will be monitored closely and who will seek care when their asthma is uncontrolled.

— Richard Saitz, MD, MPH, FACP, FASAM


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