AHC Media LLC

Vol. 18, Issue 8, November 2010
www.ahcmedia.com

Critical Care [ALERT]

A monthly update of developments in critical care and intensive care medicine

ABSTRACT & COMMENTARY

Should We Paralyze Patients with Severe Acute Respiratory Distress Syndrome?

By Andrew M. Luks, MD
Pulmonary and Critical Care Medicine, University of Washington, Seattle
Dr. Luks reports no financial relationship to this field of study.

SYNOPSIS: The multicenter, randomized trial demonstrated that 48 hours of treatment with cis-atracurium in patients with ARDS and a P/F ratio below 150 mm Hg resulted in improvements in adjusted 90-day mortality and time off the ventilator without increasing the incidence of ICU-acquired paresis.

SOURCE: Papazian L, et al; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-1116.

Paralytic agents such as vecuronium and cis-atracurium have been used as "rescue therapies" in patients with ARDS for many years, but, as with other rescue strategies including prone mechanical ventilation or inhaled vasodilators, evidence of a mortality benefit from this intervention has been lacking. Building on a prior study of theirs demonstrating that a 48-hour infusion of cis-atracurium was associated with improved oxygenation and a trend toward improved mortality, Papazian and colleagues conducted an adequately powered randomized trial to investigate if this therapy led to a mortality benefit without increasing the risk of ICU-acquired paresis.

They enrolled patients at 20 ICUs in France that met the consensus definition of ARDS, had a PaO_2/FIO_2 (P/F ratio) less than 150 mm Hg and had been on mechanical ventilation for < 48 hours. Subjects were randomized to receive a 15 mg bolus of cis-atracurium, followed by an infusion of 37.5 mg/hr for 48 hours, or placebo. Train-of-four monitoring was not performed and all patients

Financial Disclosure: *Critical Care Alert*'s editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, and peer reviewer William Thompson, MD, report no financial relationships to this field of study.

Critical Care [ALERT]

Critical Care Alert,
ISSN 1067-9502, is published monthly by AHC Media LLC
3525 Piedmont Road., NE
Building 6, Suite 400
Atlanta, GA 30305.

POSTMASTER: Send address changes to Critical Care Alert,
P.O. Box 740059,
Atlanta, GA 30374.

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Subscription Prices
United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling. (Student/Resident rate: $120).

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GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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in both groups were ventilated with assist-control ventilation with tidal volumes of 6-8 mL/kg. Open-label, 20 mg bolus injections of cis-atracurium were allowed in either patient group when the plateau pressure exceeded 32 cm H_2O despite increased sedation, or tidal volume modifications. Prone mechanical ventilation, inhaled nitric oxide, and almitrine mesylate (a vasodilator used in Europe) could be used at the discretion of the attending physician in either group, but no specific protocols governed the use of these therapies. The primary outcomes included death before hospital discharge and 90-day mortality, while secondary outcomes included 28-day mortality, number of days outside the ICU, ventilator-free days, and the incidence of barotrauma and ICU-acquired paresis.

One hundred seventy-eight patients were randomized to treatment with cis-atracurium while 162 received placebo. The groups were well matched except for a lower mean P/F ratio in the intervention group. Crude 90-day mortality was 31.6% in the cis-atracurium group compared to 40.7% in the placebo group (P = 0.08), while the adjusted hazard ratio for death at 90 days in the cis-atracurium group was 0.68 (95% confidence interval, 0.48-0.98; P = 0.04). Of note, improvements in mortality in the cis-atracurium group were limited to those patients with a P/F ratio < 120 mm Hg and the Kaplan-Meier curves only began to diverge after about 18-20 days. With regard to the secondary outcomes, patients in the intervention group had more ventilator-free days and days free of non-pulmonary organ failure. The incidence of pneumothorax was lower in the intervention group (4.0% vs 11.7%; P = 0.01), while the incidence of ICU-acquired paresis was no different between the two groups (~30% in each group). More patients in the placebo group received open-label cis-atracurium in the first 48 hours following enrollment while the daily sedative/analgesic doses and use of alternative rescue strategies were similar between the two groups.

COMMENTARY

This study will likely garner a significant amount of attention, as it is one of the first trials to demonstrate a mortality benefit from use of a rescue strategy in patients with ARDS and severe hypoxemia. In fact, I suspect that with the growing interest in ICU bundles and quality measures, efforts may be made to include it in revised ventilator protocols at many institutions. We need to exercise caution, however, before moving ahead in this regard. Because many problems are difficult to study in the ICU and we lack the volume of large, randomized controlled trials seen in fields like cardiology, there is a tendency in critical care medicine for positive results from single studies to be rapidly adopted into practice before further data are available. This happened with tight glucose control after a single-center study in the surgical ICU alone[1] led to widespread use of insulin drip protocols and with the use of corticosteroids in septic shock after a mortality benefit was reported in sub-group analysis in a well-publicized trial.[2] In both cases, follow-on studies subsequently questioned the benefit of those interventions or demonstrated a higher incidence of adverse events than earlier reported.

There are several issues that need to be resolved in the case of paralytic agents before we move toward wider adoption of the practice. First, the mechanism for the purported effect is unknown and as a result it falls short with regard to the question: "Does this result make sense?" We are left wondering, for example, why the survival curves do not diverge until more than 18 days from use of the therapy. When lung-protective ventilation was adopted for management of ARDS, there was a large body of animal data and preliminary studies in humans that spoke to the mechanism and demonstrated plausibility of the approach. This body of knowledge is lacking in the case of paralytics.

Second, the investigators only used cis-atracurium, and it would be

useful to know whether the benefits extend to other, less expensive paralytic agents such as vecuronium. Finally, and perhaps most important, many studies have demonstrated that use of paralytic agents is associated with an increased risk of ICU paresis, in distinction to one of the main findings in this study. Granted, the data from Papazian and colleagues were collected in a prospective, randomized manner compared to the retrospective nature of much of the other data on this issue. However, given the implications of ICU-acquired paresis for patient outcomes, it is important to validate the findings of this study with regard to the paresis issue, as it would not be in our patients' interests if, similar to the observed rates of hypoglycemia with strict glucose targets, we subsequently discovered higher than anticipated rates of ICU paresis after widespread adoption of paralytic agents. Given these outstanding issues, paralytic use in ARDS is a bandwagon we should let travel a bit further before we look to jump on. ■

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ABSTRACT & COMMENTARY

Preventing Unplanned Extubations: Pulling out the Evidence

By Ruth M Kleinpell, PhD, RN

Director, Center for Clinical Research and Scholarship, Rush University Medical Center; Professor, Rush University College of Nursing, Chicago

Dr. Kleinpell reports no financial relationship to this field of study.

SYNOPSIS: In this survey of ICU practitioners' attitudes and perceptions about the causes and consequences of unplanned extubation, most considered it to be a risk to patient safety while a minority considered it to be a medical error.

SOURCE: Tanios MA, et al. Can we identify patients at high risk for unplanned extubation? A large-scale multidisciplinary survey. Respir Care 2010;55:561-568.

This web-based survey assessed 1976 critical care practitioners' perceptions of the risks for unplanned extubation. Members of the American Association for Respiratory Care, the American Association of Critical Care Nurses, and the Society of Critical Care Medicine reported a number of factors associated with unplanned extubation, including outward migration of the endotracheal tube (ETT; reported by 73% of respondents), the patient tugging on the ETT (87%), removing a nasogastric tube (71%), absence of physical restraints (72%), a nurse/patient ratio of 1:3 (60%), trips out of the ICU for tests (59%), and light sedation (42%).

When presented with two clinical vignettes (deliberate self-extubation and accidental extubation), the majority of the 870 nurse, 605 physician, and 419 respiratory therapist respondents considered deliberate self-extubation by a low-risk patient to represent an airway accident and accidental extubation in a high-risk patient to represent an error in medical management. The results of the study provide information on risk factors for unplanned extubation that can be used to target prevention strategies to decrease the risk of adverse events.

COMMENTARY

A significant percentage of ICU patients require endotracheal intubation and mechanical ventilation. Unplanned extubation is a recognized complication that poses risks to intubated patients. The findings of the study indicate that a number of factors are perceived to be risks for unplanned extubation by critical care clinicians. Half of all respondents perceived that the definition of a near-miss for unplanned extubation depended on the patient's medical condition. The majority (95%) viewed frequent near-misses as a threat to patient safety, while only 44% considered an unplanned extubation as a medical error.

It is estimated that between 1% and 14% of patients receiving mechanical ventilation experience an unplanned extubation.[1,2] Although most studies have demonstrated that mortality

is similar in patients experiencing unplanned extubation compared to controls, there is evidence that patients who require reintubation have a significantly longer duration of ventilation, longer ICU stay, and longer hospital stay.[3] In one study of 100 patients who experienced unplanned extubation compared to 200 controls during a 5-year period in a medical surgical ICU, mortality was found to be decreased in those having an unplanned extubation compared to controls.[4] In addition to the risk factors identified by critical care clinicians in the survey, several additional factors have been associated with unplanned extubation including agitation and greater use of benzodiazepines,[2] as well as inadequate sedation, improper position of the ETT, and insecure ETT.[5,6]

While a significant percent of patients experiencing an unplanned extubation do not require reintubation, a factor associated with the need for reintubation after unplanned extubation is increasing age.[4]

Several quality improvement initiatives targeting reducing unplanned extubation in the ICU have demonstrated beneficial outcomes from educational interventions and implementation of protocols for securing endotracheal tubes.[5,7] Preventive measures such as using an experienced transport team,[8] avoiding unnecessary trips out of the ICU, and reducing unnecessary portable chest radiographs[9] may help reduce the incidence of unplanned extubations. As weaning readiness can play a role in patients that intentionally self-extubate, evaluating the need for continued intubation is a necessary component of daily spontaneous breathing trial assessments. Pulling out the evidence for prevention of unplanned extubation is not difficult, but requires ensuring clinician awareness and the use of preventive measures, in addition to preventing prolonged unnecessary intubation. ■

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ABSTRACT & COMMENTARY

Is Hyperoxia Harmful After Resuscitation from Cardiac Arrest?

By David J. Pierson, MD, Editor

SYNOPSIS: In this study from 120 hospitals in the Project IMPACT database, the presence of hyperoxia (arterial PO_2 300 mm Hg or higher) in the first 24 hours after resuscitation from cardiac arrest was associated with a worse in-hospital mortality than either normoxia or hypoxia.

SOURCE: Kilgannon JH, et al; for the Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303:2165-2171.

Project IMPACT, a proprietary database originally created by the Society for Critical Care Medicine and now maintained by Cerner Corp., collects data from a voluntary consortium of ICUs across America. In this study, Kilgannon et al used data collected from 120 Project IMPACT hospitals between 2001 and 2005 to look for associations between initial arterial PO_2 obtained in the ICU and patient outcome following resuscitation from cardiac arrest.

Data from adult patients with nontraumatic cardiac arrest, either out-of-hospital or occurring in hospitalized patients, within 24 hours of

ICU admission were examined. The presence of hyperoxia, normoxia, or hypoxia according to the first PO_2 entered into the database during the initial 24 hours in the ICU was correlated with in-hospital mortality. Hyperoxia was defined as a PO_2 of 300 mm Hg or higher; hypoxia was either a PO_2 < 60 mm Hg or PaO_2/FIO_2 (P/F) < 300 mm Hg; normoxia was either a PO_2 > 60 mm Hg or a P/F > 300 mm Hg with PO_2 < 300 mm Hg. Statistical attempts were made to control for potential confounders such as age, pre-admission functional status, comorbid conditions, and vital signs.

Of the 8736 eligible patients, 2410 did not have an arterial blood gas recorded within the first 24 hours in the ICU. Among the other 6326 patients, 1156 (18%) had hyperoxia, 3999 (63%) hypoxia, and 1171 (19%) normoxia on the initial ICU blood gas specimen. Hyperoxia was associated with higher in-hospital mortality (63%; 95% confidence interval [CI], 60%-66%) as compared to the normoxia group (45%; 95% CI, 43%-48%) and the hypoxia group (57%; 95% CI, 56%-59%). After correcting for the potential confounders, initial hyperoxia had an odds ratio for death of 1.8 (95% CI, 1.5-2.2). The authors conclude that exposure to hyperoxia following cardiac arrest is an independent predictor of a worse outcome in the form of in-hospital mortality.

COMMENTARY

The findings of this study support the notion that exposure of the brain and other tissues to hyperoxia following return of spontaneous circulation after cardiac arrest is harmful, perhaps through the generation of free oxygen radicals. Based on these findings, the authors call for clinical trials of controlled reoxygenation during the post-resuscitation period. While the results fit nicely with our concept of pathophysiology, there are a couple of troubling issues with the study with respect to its design and the potential generalizability of the findings.

The first issue is how exposure to the variable of interest was identified — both in terms of definition and with respect to duration of exposure. The 3 categories of arterial oxygenation, as determined on the first arterial blood specimen recorded after the patient arrived in the ICU, do not correspond to any physiologic categorization I can figure out. Presumably, oxygen free radicals are generated in some relation to tissue oxygen exposure — that is, to the number of oxygen molecules to which vulnerable cells are exposed. This should correlate with tissue PO_2, which would be approximated most closely by capillary oxygen content, and next best (in the absence of hemoglobin concentration) by arterial PO_2 — but not the concentration of inspired oxygen or the alveolar-to-arterial PO_2 gradient, for which P/F is a surrogate. One would expect that arterial PO_2 and not P/F would best assess the variable of interest. In the present study, however, according to the criteria used, patients in the normoxia and hypoxia groups could both have PO_2 values as high as 299 mm Hg (PO_2 between 60 and 299 mm Hg in the former, and PO_2 up to 299 mm Hg in the latter).

This concern could be addressed if the paper reported actual PO_2 values in the 3 groups, but it does not. Thus, the magnitude of differences in the variable of greatest interest among the groups, in relation to the reported outcome, is unknown. In addition, in keeping with the hypothesis being investigated, the duration of exposure to hyperoxia would be expected to be an important variable. As it is, the time from resuscitation to identification of oxygenation status is unknown, other than the patient entered the ICU within 24 hours after resuscitation and the blood gas was obtained within 24 hours after that. Presumably, the reasons for this, and for the unusual definitions used with respect to oxygenation, have to do with what was available in the database.

A second concern relates to the potential generalizability of the findings beyond the hospitals that furnished the data. Project IMPACT collects data from a voluntary consortium of ICUs rather than from a defined subset of U.S. ICUs selected by specified criteria. According to the authors, the 120 hospitals furnishing data for the present study were mainly large non-academic community hospitals. How the results of this study might apply to patients and their management in institutions with different demographics is unknown.

These concerns notwithstanding, the findings of the present study support the concept that, after resuscitation from cardiac arrest, adequate oxygenation should be provided to avoid the adverse effects of tissue hypoxia, but excessive exposure to oxygen beyond that necessary for adequate arterial oxygenation should be avoided. The study's results are consistent with the most recent recommendations of the International Liaison Committee on Resuscitation that arterial saturation be maintained between 94% and 96% following resuscitation from cardiac arrest.[1] ■

Reference

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ABSTRACT & COMMENTARY

Steroids for COPD Exacerbations: Is High-dose IV Administration Really Necessary?

By David J. Pierson, MD, Editor

SYNOPSIS: In an observational study of patients managed for COPD exacerbations in 414 U.S. hospitals, intravenous administration of corticosteroids at high doses conveyed no detectable benefits over oral administration at lower doses, although the great majority of patients received the former.

SOURCE: Lindenauer PK, et al. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. JAMA 2010;303:2359-2367.

Although corticosteroids are beneficial in treating severe exacerbations of chronic obstructive pulmonary disease (COPD), studies to date have not shown high-doses (such as methylprednisolone, 2 mg/kg or more per 24 h) administered intravenously (IV) to be superior to lower doses (e.g., prednisone, 40 mg/day) given orally, with respect to clinically important outcomes. Because of the greater patient discomfort, complications, and expense of high-dose IV steroid therapy, current American and European evidence-based practice guidelines recommend lower-dose, oral therapy in the management of COPD exacerbations. Lindenauer and colleagues carried out this study to see how often the latter was used in treating patients hospitalized for this condition, and also to determine whether there was any evidence for an advantage of higher-dose, IV steroid administration.

The authors searched a proprietary database containing data from 414 U.S. hospitals — mainly small to midsize urban, nonteaching hospitals — for patients admitted because of an exacerbation of COPD (or acute respiratory failure plus COPD) in 2006 and 2007. Of 213,917 such patients, they excluded readmissions; those with other pulmonary diagnoses such as pneumothorax, pneumonia, or pulmonary embolism; those admitted directly to the ICU; and also those who received corticosteroids during the first 2 days at dosages outside the ranges examined: low-dose 20-80 mg prednisone/day by mouth, and high-dose IV 120-800 mg prednisone-equivalent/day. After exclusions, 79,985 patients comprised the study population, 80% of whom were admitted via the emergency department.

Median age of the patients was 69 years, 61% were women, 73% were white, and most were on Medicare. Their median length of stay was 4 days and 1.4% died. The great majority (92%) received high-dose IV steroids, with a median total dose of 600 mg (prednisone equivalents) in the first 2 days compared with 60 mg in those patients who initially received oral steroids. Patients treated with low-dose oral steroids tended to be slightly older, had more comorbidities, and were given antibiotics less often. The 6220 patients who initially received low-dose oral steroids were matched individually with patients in the high-dose IV group by means of a propensity analysis. After all adjustments, these patients were not more likely to experience treatment failure (defined as initiation of mechanical ventilation after the second hospital day, mortality, or readmission for a COPD exacerbation within 30 days) than those treated with high-dose IV steroids (odds ratio, 0.93; 95% confidence interval, 0.84-1.02). Patients treated with low-dose oral steroids had shorter lengths of hospital stay and lower treatment costs. The authors conclude that, among patients hospitalized for a COPD exacerbation, low-dose steroids given orally are not associated with worse outcomes than high-dose IV steroid therapy.

COMMENTARY

This large observational study showed that the vast majority of patients hospitalized because of an exacerbation of COPD were initially treated with high doses of IV corticosteroids — in sharp contrast to the recommendations of multiple leading clinical guidelines. This practice was not associated with any detectable clinical benefit and incurred higher hospital costs and longer patient stays.

There were several other findings that I found of interest in their divergence from current recommendations for best practice in managing COPD exacerbations. Of the 213,917 patients screened for the study by virtue of having a discharge diagnosis of COPD exacerbation or acute respiratory failure, 12% never received any steroids. Only 46% of the 80,000 patients in the

final cohort had an arterial blood gas measurement during their first 2 hospital days. Long-acting beta-2 agonists (generally considered contraindicated in acute exacerbations) were administered to 40% of the patients. And only 7.3% of the cohort received non-invasive ventilation. Granted, these were patients who were not initially admitted to an ICU, and the 1.4% hospital mortality rate suggests that they did not have exacerbations as severe as those enrolled in most studies of non-invasive ventilation. Still, non-invasive ventilation is the intervention most strongly correlated with improved mortality, fewer intubations, and shorter hospital stays among patients with severe COPD exacerbations.

Why does real-world medical practice differ so markedly from the standard of care as recommended in practice guidelines? With respect to the route and dosing of corticosteroid therapy for COPD exacerbations, the authors of this study offer several possible explanations. Given that steroids hasten recovery in this condition, there may be a natural tendency to assume that larger doses will be more effective than smaller ones, and that parenteral administration will be more certain in onset and magnitude of clinical effect than oral dosing. That neither of these assumptions is true may be unknown to a substantial proportion of clinicians. Another possibility may be less potentially correctable: Some utilization review programs may require the presence of an IV line to justify continued hospitalization at an acute level of care.

Patients with COPD who present with an acute increase in dyspnea and/or sputum quantity, and/or a change in sputum color, should be evaluated clinically to make sure the cause is not pneumonia, pulmonary edema, or some process other than an exacerbation. Those diagnosed with a COPD exacerbation should be assessed for acute respiratory failure (with an arterial blood gas if this is suspected), and consideration given to initial management in the ICU. Non-invasive ventilation is indicated for severe exacerbations, particularly in the presence of acute-on-chronic respiratory acidosis. Otherwise, in addition to maintaining a oxyhemoglobin saturation of 90%-92%, evidence-based management focuses on giving short-acting bronchodilators by aerosol and corticosteroids systemically. However, unless the patient is actively vomiting or on nasogastric suction, the steroids can be low-dose (e.g., 40 mg once daily) and administered by mouth; IV administration of higher doses may increase hyperglycemia and other adverse effects, and is more expensive, but has not been shown to be any more effective. ■

CME/CNE Questions

23. In the study by Papazian and colleagues, 48-hour infusion of cis-atracurium was associated with which of the following outcomes in patients with ARDS?

a. Increased incidence of ICU paresis
b. Increased incidence of pneumothorax
c. Increased incidence of organ failure
d. Decreased adjusted 90-day mortality
e. Decreased antibiotic use

24. Which of the following has *not* been associated with unplanned extubation?

a. Patient agitation
b. Increased use of benzodiazepines
c. A decreased nurse/patient ratio
d. Inward migration of the endotracheal tube
e. None of the above

25. In the treatment of COPD exacerbations requiring acute hospitalization, which of the following statements is *true* with respect to corticosteroid therapy?

a. Because of variable gastric absorption, administration should be by IV infusion.
b. Higher doses (e.g., 300 mg/day prednisone-equivalent) decrease mortality and reduce the need for intubation compared to lower doses (e.g., 40 mg/day).
c. Both of the above
d. Higher doses are associated with more adverse effects.
e. None of the above

Answers: 23. d, 24. d, 25. d.

CME/CNE Objectives

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

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1. Publication Title	2. Publication No.	3. Filing Date
Critical Care Alert	1067-9502	10/1/10
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305

Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

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13. Publication Name: Critical Care Alert
14. Issue Date for Circulation Data Below: September 2010

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[IN FUTURE ISSUES]

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Acetaminophen toxicity

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Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

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the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■