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Critical Care [ALERT]

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

SPECIAL FEATURE

Update on Hemodynamic Monitoring in 2012

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Dr. Wall reports no financial relationships relevant to this field of study.

Hemodynamic monitoring is an essential part of caring for critically ill patients. Critical care providers are regularly faced with the challenge of determining whether a patient is adequately volume resuscitated, and hemodynamic assessments are often the first step in making a proper diagnosis so that other life-saving therapies can be promptly implemented. The purpose of this review is to provide an overview of available hemodynamic monitoring systems, and offer general principles to guide providers who are trying to choose the best system for their particular setting.

All of us know that initial uncertainty when an obese, hypotensive patient with renal failure and/or cardiomyopathy rolls into the unit. Do they need more fluid? Are they bleeding? Could it be tamponade or a pulmonary embolism? Should we check central venous pressure (CVP) or place an arterial line? What about a pulmonary artery (PA) catheter? Should we try the newer less invasive cardiac output (CO) monitors? Would measurement of mixed venous oxygen saturation (SvO_2) help, and should it be done continuously or intermittently? What about bedside ultrasound? How about another fluid challenge or vasopressors?

CARDIAC OUTPUT HEMODYNAMIC MONITORING DEVICES

While microcirculatory changes are thought to be the main culprits of organ dysfunction in shock, the reality is that technologies for monitoring microcirculation are not readily available. This disconnect has resulted in a myriad of CO (i.e., macrocirculation) monitoring devices. The choices are overwhelming. While a detailed review of every system is beyond the scope of this article, I

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will briefly discuss the most popular types of systems. I will also discuss two commonly used CO surrogates: CVP and SvO_2.

PULMONARY ARTERY CATHETER

The PA catheter has long been the bedside "gold standard" for hemodynamic monitoring. It relies on the thermodilution technique, wherein downstream temperature changes are used to calculate CO. The advantage of the PA catheter is that it also allows measurement of CVP, PA pressure, systemic vascular resistance, cardiac filling pressures, and SvO_2.

Despite an incredible array of data, studies have failed to show that placing a PA catheter improves patient outcomes.[1,2] In addition, key information gleaned from the PA, namely CVP and filling pressures, do not adequately predict fluid responsiveness in hemodynamically unstable patients. Moreover, these devices are occasionally associated with serious complications including pneumothorax, arrhythmias, heart block, and PA rupture/infarction. For all of these reasons, use of PA catheters has dramatically waned in recent years. Nonetheless, most other CO monitoring devices still use the PA catheter as their reference validation standard.

LESS INVASIVE MONITORING SYSTEMS

Several new less invasive monitoring systems are available as alternatives to the PA catheter. These include the LiDCO™ Plus, PiCCO™, COstatus™, Vigileo™, MostCare™, and Flo Trac™ systems. Each system uses arterial analyses to continuously measure pulse pressure variation (PPV) and stroke volume variation (SVV). Each requires some sort of arterial line, and most also require a central venous line for calibration.

These systems use basic principles of dilution to estimate CO, similar to the PA catheter. The PiCCO uses injections of ice-cold intravenous fluids as the indicator, measuring downstream temperature changes. The LiDCO uses trace amounts of lithium chloride as the indicator, using a lithium-sensing electrode. The COstatus system calculates CO using ultrasound technology to measures changes in blood velocity following an injection of warm saline.

These new technologies have limitations. Although PPV and SVV are decent tools for predicting fluid responsiveness,[3] there are no studies showing these new systems save lives or reduce length of stay. Furthermore, these systems are limited by factors that alter arterial waveform such as atrial arrhythmias, severe atherosclerosis, and aortic regurgitation. The Vigileo and MostCare systems do not calibrate via a central venous catheter but instead rely on proprietary software and make different assumptions to accomplish this goal. As a result, data cannot be superimposed from one system to another. Finally, PPV and SVV have only been validated for predicting fluid responsiveness in mechanically ventilated patients who are not initiating breaths on their own. A prior review discusses several of these issues in greater detail.[4]

ECHOCARDIOGRAPHY AND ULTRASOUND

At the bedside, echocardiography is a useful diagnostic tool because it can visualize cardiac chambers, valves, pericardium, and overall cardiac function. In turn, these images can guide therapy. For example, small ventricles might prompt a fluid challenge. A poorly contractile myocardium might prompt a trial of dobutamine. A dilated right ventricle would suggest pulmonary embolism or inferior infarction. Valvulopathy and tamponade can be quickly determined.

Echocardiography is also helpful because it uses Doppler-based methods to calculate CO. This is achieved by directing the ultrasound beam along the aorta. The moving red blood cells create a resultant Doppler frequency that can be used to measure flow velocity and volume, and thereby CO.

Several trends are escalating the use of bedside ultrasound in the intensive

care unit (ICU). First, general ultrasound skills are now being taught in critical care fellowships, and intensivists are increasingly expected to have basic bedside ultrasound skills. Second, technologic advances have made bedside ultrasound devices affordable and portable. As a result, repeated assessments throughout the day are no longer an unrealistic goal.[5,6] In the coming decade, I suspect that bedside ultrasound will become nearly as ubiquitous as the stethoscope in the ICU. An explosion of educational courses and online offerings are available.

Like every technology, echocardiography has limitations. Although fairly accurate for CO calculations, the technology requires training and is operator-dependent. In addition, echocardiography can only provide a CO snapshot. Serial and/or continuous measurements will require the clinician to spend longer amounts of time at the bedside. Furthermore, transthoracic techniques do not always yield good images and the effort/risk of transesophageal echocardiography restricts its availability.

MIXED VENOUS OXYGEN SATURATION

SvO_2 reflects the balance between oxygen delivery and oxygen consumption (VO_2). It depends on arterial blood saturation (SaO_2), the balance between VO_2 and CO, and hemoglobin (Hgb) levels. It can be explained by the Fick equation:

$$SvO_2 = SaO_2 - \frac{VO_2}{CO \times Hgb}$$

Looking at the equation, a few simple observations can be made. If CO increases and everything stays the same, then SvO_2 increases. If increased VO_2 is not compensated by increased CO, then SvO_2 will drop. If SaO_2 increases (e.g., higher FiO_2 on the ventilator), then SvO_2 will increase. If tissues are not capable of extracting oxygen (e.g., in the case of cell death), then SvO_2 may remain high.

A true SvO_2 must be drawn from the PA. Since PA catheters have become unpopular, most providers simply opt for a subclavian or internal jugular central venous catheter with its tip in the superior vena cava. Such a sample is called a central venous oxygen saturation ($ScvO_2$). The two values are not the same and there is debate about their interchangeability.[7] In addition, the relationship between CO and venous saturations is imperfect.[8]

Despite these limitations, monitoring of the $ScvO_2$ is often used during resuscitation of patients with septic shock. In early goal-directed resuscitation of septic patients, there was an association between higher $ScvO_2$ values and lower mortality.[9] The Surviving Sepsis Campaign suggests a target $SvO_2 \geq 70\%$ or $ScvO_2 \geq 65\%$.[10] Real-time $ScvO_2$ values can be continuously displayed using a specialized catheter that hooks up to the bedside monitor. No study has systematically compared continuous vs intermittent measurements of SvO_2/$ScvO_2$.

A high SvO_2 is not always a good thing. It does not always signify adequate perfusion. Indeed, a high SvO_2 may represent maldistrubution of peripheral blood flow and/or impaired oxygen extraction in the tissues. In septic shock, patients often have high CO and low oxygen extraction capabilities, resulting in a high SvO_2. Such patients often respond favorably to additional fluid, even though their mixed venous saturations are normal-to-high.[11]

In summary, the SvO_2 and $ScvO_2$ are useful but imperfect indicators of cardiac output. Low venous saturations are an important warning sign for inadequate oxygen delivery. Low values should prompt the clinician to search for an underlying metabolic or circulatory impairment. The SvO_2 and $ScvO_2$ are probably most useful during the early phases of disease and resuscitation.

BIOIMPEDANCE AND BIOREACTANCE

Bioimpedance describes the response of a living organism to an externally applied electric current. It refers to the opposition to flow of that current through tissues (i.e., the opposite of conductivity). Bioreactance is an extension of this concept. It measures the change in frequency of current traversing tissue, rather than changes in impedance.

These techniques are simple to initiate, safe and non-invasive. Electrodes are placed on the patient's body, and a high-frequency, low-magnitude alternating current passes through the thorax. The impedance of this current changes as blood flow varies during the cardiac cycle. For several decades, bioimpedance technology has been used to measure CO in the perioperative setting.

Unfortunately, the technology is not reliable in critically ill patients.[12] Electrical conductivity varies when patients spontaneously breathe. In addition, conditions such as obesity and chronic obstructive pulmonary disease cause changes in thoracic and/or vascular geometry that introduce error. For these and other reasons, bioimpedance has little utility in the ICU.

GENERAL PRINCIPLES OF HEMODYNAMIC MONITORING

If you are hoping to discover a perfect hemodynamic monitoring technology, I have

Table. General Principles When Using Hemodynamic Monitors

- Medical devices don't save lives.
- Monitoring requirements change during an illness.
- Every patient has different hemodynamic goals.
- Don't rely on just one variable.
- A high cardiac output and high SvO_2 are not always best.
- Monitor hemodynamic changes over short periods of time.
- The cardiac output is estimated, not measured.
- Continuous measurement is preferable.
- Non-invasiveness is not the only goal.

(Table adapted from Vincent JL, et al.[13])

bad news — it doesn't exist. Despite seductive marketing and high prices, every hemodynamic monitor is imperfect. In addition to scrutinizing the actual technologies, providers need to consider some principles inherent to using these imperfect tools (*see Table*). A recent review discusses several of these principles in greater detail.[13]

1. Devices don't save lives. A medical device can't improve outcomes unless it is coupled with a treatment that also improves outcomes. In other words, if a hemodynamic monitoring device doesn't change behavior, it will not save lives. The data from the device must be accurate, readily available, interpretable, relevant, and responsive to change. The clinician must know how to properly apply a life-saving therapy based on the data.

2. Monitoring requirements will change during an illness. The initial monitoring system(s) must be selected based on the patient's specific needs. In many patients, an invasive approach (i.e., central venous catheter and arterial line) are needed. Once a patient stabilizes, less-invasive monitoring can be employed. Although studies failed to show a benefit for routine placement of PA catheters in the resuscitation of all critically ill patients, the PA catheter still has a role in managing selected complex cases.

3. Every patient will have different hemodynamic goals. It is unwise to universally resuscitate every patient with septic shock to a systolic pressure of 90 mmHg or CVP of 8-12 mmHg. The optimal hemodynamic targets will vary depending on age and comorbidities. Consider multiple factors in addition to the hemodynamic monitor's data. If the CVP remains low in a patient that you think is adequately resuscitated, don't reflexively give more fluid.

4. Don't rely on just one variable. Combine and integrate all available information. Use multiple monitors and tools. The differential diagnosis for a hypotensive patient with low CO is very different than for a hypotensive patient with high CO.

5. A high CO and high SvO_2 are not always the best goals. Excessive administration of fluids can result in volume overload and edema, whereas excessive pressors can be detrimental in patients with coronary disease. Although Rivers noted an association between higher SvO_2 and lower mortality in sepsis patients,[9] that was a single-center study and their finding may not be reproducible in other settings or populations.

6. Monitor hemodynamic changes over short periods of time. For critically ill patients, there is usually more value in monitoring acute CO changes after administration of a therapy. Comparing slow changes in CO over several days is less relevant in most non-cardiac patients.

7. The cardiac output is estimated, not measured. No bedside monitor actually measures CO. For this reason, agreement of values obtained with different devices is relatively poor. The accuracy of absolute values is less important when following trends, however. A slightly less accurate value obtained by a less-invasive technique may be preferable if it can be obtained more rapidly and easily.

8. Continuous measurement is preferable. Although there is no study proving that continuous CO monitoring is superior to intermittent monitoring, continuous systems make more sense. We already routinely monitor numerous other hemodynamic variables in a continuous manner. Systems with intermittent data or requiring constant recalibration may not provide the real-time data needed for optimal management of critically ill patients.

9. Non-invasiveness is not the only goal. I agree with a prior review that recommends caution when implementing newer less invasive systems.[4] Use the proper tool at the proper time to answer the proper question.

CONCLUSION

The number of choices for hemodynamic monitoring devices continues to grow. Every device has limitations, and a "perfect device" will never exist. If able, use a combination of devices, both invasive and non-invasive. Be flexible in your approach and reassess complex patients repeatedly throughout the day. When different data contradict each other, fall back on your training. Trust your intuition. ■

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ABSTRACT & COMMENTARY

Does the Use of Protocols in the ICU Interfere with Learning?

By David J. Pierson, MD, Editor

SYNOPSIS: This study of first-time takers of the American Board of Internal Medicine's critical care certifying examination found no relationship between performance on questions related to mechanical ventilation and the intensity of exposure to mechanical ventilation protocols during fellowship training.

SOURCE: Prasad M, et al. Clinical protocols and trainee knowledge about mechanical ventilation. *JAMA* 2011;306:935-941.

Prasad and associates conducted a retrospective cohort study of associations between internal medicine trainee exposure to mechanical ventilation protocols and their performance on questions related to this topic on the critical care board-certifying examination. These same investigators had previously conducted a survey on the availability of mechanical ventilation protocols in the ICUs of U.S. teaching hospitals.[1] In this study, the authors used data from that survey to assess critical care fellows' exposure to protocols in the ICUs in which they trained, matched with performance data on questions pertaining to mechanical ventilation on the American Board of Internal Medicine's critical care medicine certifying examinations administered in 2008 and 2009. Only the examination results from intensivists from training programs that participated in the previous survey were included, and only data from first-time test takers were used.

Of the 88 critical care medicine training programs whose graduates took the certifying examination, 27 (31%) had no protocols for ventilator weaning, sedation management in ventilated patients, or lung-protective ventilation for managing acute lung injury. Nineteen programs (22%) had 1 such protocol, 24 (27%) had 2, and 18 (20%) had 3 protocols for at least 3 years. Programs were designated as providing high-intensity protocol exposure if they had 2 or more protocols in place for at least 3 years (42 programs, 48%), or low-intensity protocol exposure if they had 1 or 0 protocols (46 programs, 52%).

Of the 778 examinees for the 2 years, 553 (71%) were included in the study by virtue of having trained at a program responding to the previous survey. These examinees were statistically indistinguishable from the others with respect to performance on the examination. Overall, 91% of the examinees in the study passed, and no differences were detected in performance on mechanical ventilation-related questions with respect to protocol exposure during training. Multivariable analysis for potential confounders, such as examination year, exam score, and country of birth and residency training, showed no differences associated with mechanical ventilation knowledge. Thus, the investigators were unable to demonstrate any evidence of a detrimental effect of protocol use on trainee learning with respect to mechanical ventilation.

COMMENTARY

The barriers between evidence and actual practice are numerous and complex, and protocols are one acknowledged means for overcoming them.[2,3] Protocols have been shown to decrease practice variation in numerous health care settings and to be associated with improved patient outcomes for several aspects of critical care, including mechanical ventilation. Many protocols empower non-physicians (such as nurses and respiratory therapists) to assess patients for manifestations of illness and responses to interventions, and to initiate, adjust, or discontinue therapy within boundaries established by the institution for the protocol. By turning moment-to-moment decision-making over to clinicians other than physicians, it may be hypothesized that such protocols remove a level of involvement for physician trainees and thus interfere with learning. This study tested this hypothesis and found solid evidence to refute it.

Only one previous study has looked at this issue. In 2000, Stoller and colleagues published a study of medicine house-officers' knowledge of respiratory care practices in two academic centers, one in which respiratory care protocols were extensively used and one without such protocols.[4] Internal medicine residents were studied at the Cleveland Clinic, where multiple respiratory care protocols had been used for years and were incorporated into trainee education, and also at the University of Nebraska, where there were no such protocols. Residents representing all 3 training years answered multiple-choice questions related to whether various respiratory care modalities should be administered to the patients in 5 clinical vignettes. The trainees at both institutions got about three-fourths of the questions right, with no detectable differences between the training programs except that residents at the Cleveland Clinic scored statistically better on the questions relating to one of the vignettes.

Only about a third of each program's residents were included in the study, and there are likely many differences between the trainees and the programs at the participating institutions, in addition to whether respiratory care protocols are in use. In addition, the Stoller study[4] dealt with respiratory care treatments not involving mechanical ventilation. Nonetheless, it represented the first attempt to address concerns about potential adverse effects of protocolized care on trainee learning.

The present study by Prasad et al focused on mechanical ventilation, employed a much more rigorous study design, and examined trainee knowledge much more comprehensively. It makes an important contribution to education in the critical care setting by reassuring all concerned that the use of protocols does not interfere with trainee learning. Most likely, institution-specific, evidence-based protocols that are tailored to local patient populations and practice patterns actually facilitate learning, by permitting trainees to observe best practices and reducing the opportunity for adverse consequences of a more trial-and-error approach. ■

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ABSTRACT & COMMENTARY

Insurance Status and ICU Outcomes

By David J. Pierson, MD, Editor

SYNOPSIS: In this study of a statewide administrative database, among 138,720 adult patients admitted to an ICU, uninsured patients had a 25% higher likelihood of death within 30 days compared with privately insured patients, differences that persisted after multiple adjustments for demographics, severity of illness, and site of care. Uninsured patients received central venous catheterization, acute hemodialysis, and tracheostomy significantly less often than insured patients.

SOURCE: Lyon SM, et al. The effect of insurance status on mortality and procedural use in critically ill patients. *Am J Respir Crit Care Med* 2011; 184:809-815.

Lyon and colleagues performed a retrospective cohort study of the relationship between insurance status and 30-day mortality, as well as the use of five common ICU procedures, among 138,720 adult patients admitted to ICUs in Pennsylvania in fiscal years 2005 and 2006. The primary information source was discharge data from the Pennsylvania Health Care Cost Containment Council, a nonprofit government agency that tracks all hospitalization in the state. Patients aged 65 years and older, as well as those with Medicare, military, or VA insurance were excluded, and only initial ICU admissions were used. The authors performed extensive epidemiological and statistical procedures to exclude confounders such as demographics, economic status (from zip codes), admission source and type, primary diagnosis, comorbidities, mechanical ventilation, and severity of illness on presentation. The primary outcome was 30-day mortality, and secondary outcomes were the use of central venous catheterization (CVC), pulmonary artery catheterization (PAC), acute hemodialysis, tracheostomy, and bronchoscopy.

Of the 138,720 qualifying patients, 69.2% were privately insured, 26.6% had Medicaid, and 4.2% (5814 individuals) were uninsured. Uninsured patients, as well as those on Medicaid, were widely distributed among the 169 hospitals and differed from each other. Uninsured patients were more often admitted to small community hospitals, while Medicaid patients were more often admitted to larger academic hospitals.

Absolute 30-day mortality was 4.6% for insured patients, 5.7% for uninsured patients, and 6.4% for Medicaid patients. The unadjusted odds ratio (OR) for death among patients without insurance was 1.26 (95% confidence interval [CI], 1.12-1.41; $P < 0.001$) compared to patients with insurance. This increased odds of death persisted after adjustment for all the variables used (OR, 1.25; 95% CI, 1.04-1.51; $P = 0.020$). Medicaid patients also had increased 30-day mortality (OR, 1.42; 95% CI, 1.35-1.50, $P < 0.001$), but this difference disappeared with adjustment for patient characteristics. The absolute risk difference for death, uninsured vs insured patients, was 0.01 ($P = 0.011$), meaning that for every 1000 patients admitted to an ICU in Pennsylvania during the study period, there would be 10 more deaths if all those patients were uninsured.

Uninsured patients were significantly less likely to receive CVC (OR, 0.84; 95% CI, 0.72-0.97; $P = 0.018$), acute hemodialysis (OR, 0.59; 95% CI, 0.39-0.58; $P = 0.016$), and tracheostomy (OR, 0.43; 95% CI, 0.29-0.64; $P < 0.001$). Differences for PAC and bronchoscopy were nonsignificant. Medicaid patients were significantly more likely to receive CVC, acute hemodialysis, and tracheostomy, and these differences persisted with the adjustments; differences for PAC and bronchoscopy were nonsignificant.

COMMENTARY

Compared to patients with private insurance, uninsured patients who are hospitalized acutely have higher overall mortality, but whether this is due to patient factors other than the acute illness (such as socioeconomic factors, comorbidities, or higher severity of illness on presentation), or to being treated differently in the hospital, is unclear. Further, whether any differences in outcomes are due to between-hospital differences (that is, the uninsured tending to be admitted to hospitals that provide poorer care) or within-hospital differences (that is, the uninsured tending to be treated differently from insured patients at the same hospital) has not previously been investigated. This study by Lyon et al carefully excluded differences in patient characteristics, accounting for within-hospital care and outcomes — and showed that uninsured ICU patients still had higher mortality. Such was not the case with the Medicaid patients, another group with known poorer outcomes, for whom the mortality differences disappeared when patient characteristics were considered. The authors also demonstrated that, other factors being equal, uninsured patients were less likely to get a CVC or a tracheostomy, or to undergo acute hemodialysis, than their counterparts with private insurance —again, these differences not being due to being less sick or cared for in different hospitals.

The findings of this study are unlikely to please clinicians. Surely uninsured patients have worse outcomes because they neglect their health in addition to not buying health insurance, and have more comorbidities; they wait until they are more seriously ill, and thus less likely to recover, before seeking medical attention; and they tend to be hospitalized in lower-quality institutions that have worse outcomes for everyone. According to this study, which examined those issues and others, none of the above assumptions is true. Uninsured patients, cared for in the same ICUs of the same hospitals as insured patients, undergo at least three common critical care procedures less frequently and are more likely to die. Lyon et al make no attempt to link the last two findings, since proof that ICU procedures improve outcomes is generally lacking. They also do not

attempt to explain why, within a given institution, uninsured patients might be treated differently, whether for institutional or health system reasons, or because of the actions of individual clinicians, or for some other reason. That important question must await further research. ■

CME/CNE Questions

1. Which one of the following is true about non-invasive cardiac output (CO) monitors?

a. These devices are more accurate than invasive CO monitors.
b. The systems use thermodilution techniques to estimate CO.
c. Most systems require a pulmonary artery catheter.
d. Studies have shown that these systems can reduce mortality in septic patients.
e. Data from one system can be superimposed to another system.

2. Which one of the following is true about mixed venous oxygen saturation (SvO_2)?

a. SvO_2 is ideally obtained from the superior vena cava.
b. A higher SvO_2 is always better in septic shock.
c. Studies have shown that continuous SvO_2 measurements are superior to intermittent measurements.
d. Increasing cardiac output will always increase the SvO_2.
e. SvO_2 reflects the balance between oxygen delivery and oxygen consumption.

3. Based on the study of critical care certifying examination performance with respect to trainee exposure to mechanical ventilation protocols:

a. those exposed to protocols during training had higher overall exam scores.
b. those exposed to protocols during training had lower overall exam scores.
c. those exposed to protocols during training scored higher on mechanical ventilation questions.
d. those exposed to protocols during training scored lower on mechanical ventilation questions.
e. there were no differences for either overall exam scores or mechanical ventilation questions according to whether the trainee had been exposed to protocols.

4. Most of the training programs of the examinees in the critical care certifying examination included exposure to at least which one of the following protocols?

a. Weaning from mechanical ventilation
b. Lung-protective ventilation for patients with acute lung injury
c. Use of sedation during mechanical ventilation
d. All of the above
e. None of the above

5. Which of the following statements is true about outcomes for uninsured ICU patients as compared to those with private insurance?

a. They have the same overall mortality
b. They receive central venous catheters and tracheostomies more often
c. They have higher severity of illness at the time of admission
d. All of the above
e. None of the above

6. After admission to an ICU, which of the following patient groups had higher 30-day mortality when corrected for severity of illness, comorbidities, and other patient characteristics?

a. Uninsured patients
b. Medicaid patients
c. Both a and b
d. Patients with private insurance
e. None of the above – there were no differences after the corrections

7. Uninsured patients admitted to an ICU received which of the following, as compared to insured patients?

a. More central venous catheterizations
b. More tracheostomies
c. More acute hemodialysis
d. All of the above
e. None of the above

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.

[IN FUTURE ISSUES]

Initial VAP antibiotic choice and patient outcomes

When patients with COPD exacerbations fail noninvasive ventilation

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

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In this issue: New indication for rivaroxaban; new study on warfarin testing; medications causing adverse drug events; niacin as an add-on therapy; and FDA actions.

Rivaroxaban for atrial fibrillation patients

Rivaroxaban (Xarelto), Janssen Pharmaceutical's once-a-day oral Xa inhibitor, has been approved for reducing the risk of stroke in patients with atrial fibrillation. The drug was previously approved for prophylaxis of deep vein thrombosis in patients undergoing hip or knee replacement. Rivaroxaban is the second "non-warfarin" oral anticoagulant to be approved for this indication after the direct thrombin inhibitor dabigatran (Pradaxa). The approval was based on the ROCKET AF trial, a double-blind, randomized, noninferiority comparative trial with warfarin, which showed a rate of stroke or systemic embolism of 2.1% per year for rivaroxaban and 2.4% per year for warfarin. The study looked at 14,000 patients over 700 days of follow-up. Rates of major and non-major bleeding were the same with the two drugs, although the rate of intracranial hemorrhage was lower for rivaroxaban while the rate of GI bleeding was lower with warfarin. ROCKET AF showed noninferiority of rivaroxaban vs warfarin but not superiority (*N Engl J Med* 2011;365:883-891). The approval sets up a major marketing showdown between Janssen and Boehringer Ingelheim, the manufacturer of dabigatran, for this multibillion dollar market. Meanwhile, Pfizer and Bristol-Myers Squibb are jointly developing a third drug — apixaban, also a factor Xa inhibitor — which is undergoing an "accelerated review" by the FDA with approval likely in March 2012. All three drugs have the potential disadvantage of the lack of an antidote, a problem that seems to be plaguing dabigatran with more than 250 fatal bleeding episodes reported worldwide since the drug was approved in 2010. A recent report suggests that prothrombin complex concentrate may be an effective reversal agent for rivaroxaban but not dabigatran (*Circulation* 2011;124:1573-1579). ■

Warfarin testing every 12 weeks?

One of the major disadvantages of warfarin over the newer anticoagulants is the need for frequent prothrombin time monitoring and dose adjustment. Most guidelines recommend a maximum interval of 4 weeks between testing. A new study suggests that stable patients may be safely tested at 12-week intervals. A total of 226 patients who were on a stable dose of warfarin for at least 6 months were assigned to testing every 4 weeks, while the other half had blood tests done every 4 weeks, but sham INRs within the target range were reported for two of the three 4-week periods. The percentage of time in the therapeutic range was 74.1% in the 4-week group compared with 71.6% in the 12-week group (noninferiority $P = 0.020$ for a 7.5% point margin). Patients in the 12-week group had fewer dose changes and secondary outcomes, including major bleeding, thromboembolism, and death that were no different between the two groups. The authors conclude that assessment of warfarin dosing every

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12 weeks seems to be safe and noninferior to assessment every 4 weeks, although they recommend further study (*Ann Intern Med* 2011;155:653-659). This study is important given the marked cost differential between warfarin and dabigatran or rivaroxaban. Some patients, especially if they pay for their own medications, may opt to remain on warfarin if they are on a stable dose, especially if they only require testing four times a year. ■

Adverse drug events in the elderly

Although low cost, warfarin remains one of the most dangerous medications in common usage. In fact, hospitalizations for adverse events in the elderly are much more likely to be caused by commonly used medications, such as warfarin, rather than medications classified as high risk in the elderly, according to a new study from the CDC. Researchers used a national database of adverse drug events from 2007-2009 to estimate the frequency and rates of hospitalization after emergency department visits for adverse events in older adults to assess the risk of specific medications causing this hospitalization. It is estimated that adverse drug events led to nearly 100,000 hospitalizations during the 2-year period with nearly half among adults 80 years of age or older. Nearly two-thirds of the hospitalizations were due to unintentional overdoses. Four medications or medication classes were implicated alone or in combination in 67% of hospitalizations including warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). High-risk medications were implicated in only 1.2% of hospitalizations. The authors suggest that efforts to promote the safe management of antithrombotic and antidiabetic agents have the potential to substantially reduce harm to our older patients (*N Engl J Med* 2011;365:2002-2012). This study points out that we may be spending too much effort in managing "high-risk" medications in the elderly, while warfarin alone is responsible for a third of medication-related hospitalizations. ■

Is it time to retire niacin?

An editorial published online in the *New England Journal of Medicine* asks, "Niacin at 56 Years of Age — Time for an Early Retirement?" Retirement may be the logical next step after publication of the AIM-HIGH trial (see *Pharmacology Watch* July 2011), the National Heart Lung and Blood Institute's trial comparing niacin plus intensive statin therapy with intensive statin therapy alone in patients with established cardiovascular disease. The study was halted early when it was found that the addition of 1500-2000 mg of niacin per day to simvastatin, despite significantly raising HDL levels an average of 7 points, had no effect on the primary endpoint, which was a composite of the rate of death from coronary artery disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (primary endpoint 16.4% niacin group, 16.2% placebo group; $P = 0.79$) (*N Engl J Med* published online November 15, 2011). The accompanying editorial suggests there is lack of evidence to support niacin as an add-on therapy in patients with cardiovascular disease who have well-controlled LDL cholesterol levels. Additionally, long-acting niacin is relatively expensive and frequently causes flushing — two additional factors that argue against continued use of the drug except, perhaps, in patients who are intolerant of statins (*N Engl J Med* published online November 15, 2011). ■

FDA actions

The news isn't much better for fenofibrate. The FDA has issued a safety communication for the cholesterol lowering medication stating that the drug may not lower the risk of major cardiovascular events based on data from the ACCORD Lipid trial. ACCORD (similar in design to AIM-HIGH) evaluated the efficacy and safety of fenofibrate plus simvastatin vs simvastatin alone in patients with type 2 diabetes. There was no significant difference in the risk of experiencing a major adverse cardiac event between the two groups, and women may have even experienced an increase in the risk for major adverse cardiac events with combination therapy vs simvastatin alone. The FDA is requiring the manufacturer of Trilipix brand fenofibric acid to conduct a clinical trial to evaluate the cardiovascular effects of the drug in patients at high risk for cardiovascular disease who are already taking statins (www.fda.gov/Drugs/DrugSafety/ucm278837.htm).

The FDA has approved a new formulation of zolpidem for treatment of insomnia in patients who wake up in the middle of the night and have difficulty returning to sleep. Zolpidem, originally marketed as Ambien and now available as a generic, is a short-acting hypnotic. The new product is a lower dose sublingual formulation that comes in a 1.75 mg dosage recommended for women and 3.5 mg for men. The lower dose for women is recommended because women clear the drug more slowly than men. It can be used if the patient has at least 4 hours of bedtime remaining. Zolpidem sublingual is marketed by Transcept Pharmaceuticals as Intermezzo. ■