AHC Media

Vol. 21, Issue 8, November 2013
www.ahcmedia.com

Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Procalcitonin in Sepsis: Is it Ready for Prime Time?

By Betty Tran, MD, MS
Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago

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

Although mortality rates for sepsis have improved over the past two decades, its increasing incidence has resulted in a tripling of the number of in-hospital deaths related to sepsis over the same time period.[1] Specific blood biomarkers are currently being studied with hopes that their use may improve our ability to distinguish between the systemic inflammatory response syndrome (SIRS) and sepsis, risk-stratify patients to facilitate early and appropriate triage and therapeutic decisions, and avoid the misuse and overuse of antibiotics. Procalcitonin (PCT) currently is the most studied. Its synthesis and secretion are upregulated by bacteria-specific proinflammatory mediators such as interleukin-1b, interleukin-6, and tumor necrosis factor-α, and subsequently decrease with recovery from bacterial infections. In addition, the expression of PCT is attenuated by cytokines typically released during viral infections, such as interferon-γ, and is overall not affected by medications such as steroids. PCT theoretically holds promise, but is there evidence to show that it should be a part of the medical management of all patients presenting with sepsis, and if so, in what capacity? This article aims to provide a current overview of the evidence for PCT in the diagnosis, risk stratification, and antibiotic treatment algorithms of patients presenting with sepsis in the ICU. Although PCT has also been studied in specific settings such as in patients with respiratory infections and in situations outside of the ICU, these topics are outside the scope of this overview.

PROCALCITONIN AS A DIAGNOSTIC MARKER FOR SEPSIS

It is widely accepted that early recognition and initiation of appropriate antibiotics in sepsis

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

Critical Care [ALERT]

Critical Care Alert,
ISSN 1067-9502, is published monthly by AHC Media LLC,
One Atlanta Plaza
950 East Paces Ferry Road NE
Suite 2850
Atlanta, GA 30326.

POSTMASTER: Send address changes to Critical Care Alert,
P.O. Box 550669,
Atlanta, GA 30355.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
neill.kimball@ahcmedia.com

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

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. 1-9 additional copies: $215 each; 10 or more copies: $191 each.

Back issues: $40 Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add GST and $30 shipping. Elsewhere: Add $30 shipping.

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

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity has been approved for 13.3 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider #14749, for 13.3 Contact Hours. This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

are paramount to improved patient outcomes.[2] Distinguishing between SIRS and sepsis, however, is often difficult as patient-presenting symptoms are nonspecific, current microbiologic testing has low sensitivity and inherent delays, and no gold standard ultimately exists. The latter characteristic also makes it difficult to conduct studies evaluating PCT as a diagnostic test for sepsis in critically ill patients. Overall, data have been mixed.[3-5] In the most recent meta-analysis, which also used the most stringent quality control methods, pooled sensitivity for PCT in the diagnosis of sepsis was 0.77 (95% confidence interval [CI], 0.72-0.81), specificity was 0.79 (95% CI, 0.74-0.84), with an area under the receiver operator characteristic curve (AUC) of 0.85 (95% CI, 0.81-0.88).[5] The authors only included studies with a well-defined reference standard of sepsis based on established definitions by the American College of Chest Physicians, the Society of Critical Care Medicine, or the German Sepsis Society, although diagnostic threshold values for PCT ranged considerably in all studies, from 0.25-5.79 ng/mL.[5] Similar sensitivity, specificity, and AUC were also found in two subsequent single-center studies performed in Korea[6] and the United Kingdom,[7] with PCT cutoff values of 0.2 ng/mL and 1.0 ng/mL, respectively; negative predictive values ranged from 67-99% depending on the severity of sepsis and presence of organ dysfunction.

Although these statistics show that PCT may reasonably distinguish between SIRS and sepsis given the lack of a gold-standard diagnostic test, there are several pertinent questions that need to be addressed before recommending the widespread use of PCT as a diagnostic marker: 1) are its test characteristics (especially negative predictive value) sufficient to direct medical decision making in the setting of sepsis, and 2) is it significantly better than clinical judgment? For example, is the value of PCT alone enough to persuade a clinician to hold antibiotics in a critically ill patient being admitted for suspected sepsis without a confirmed infectious source?

In the PRORATA trial, a multicenter, randomized, controlled trial to evaluate the use of a PCT-guided antibiotic strategy vs standard care on patient mortality and antibiotic-free days, approximately 30% of physicians "broke protocol" by immediately giving antibiotics to patients in whom they could not rule out infection.[8] In another multicenter, randomized, controlled trial from Belgium of PCT-guided vs standard antibiotic care, clinical judgment also superseded protocol recommendations based on PCT values as 53.7% of patients with low PCT levels (< 0.25 µg/L) were nevertheless started on antibiotics. The majority of these treatments (30/43, 69.8%) were later confirmed as correct by infectious disease specialists reviewing the charts who were blinded to the PCT results. Furthermore, 33.8% of cases in which no infection was confirmed had PCT values > 1 µg/L and 14.9% of cases with confirmed infection had a PCT level < 0.25 µg/L, for a resulting AUC of 0.69. The authors concluded that these values were "too low to propose PCT as a marker of infection in ICU patients, at least in the setting of deciding whether to initiate or withhold antibiotics."[9]

PROCALCITONIN AS A PROGNOSTIC MARKER IN SEPSIS

The ability to risk-stratify patients with sepsis has important clinical implications. Accurate prognostication not only could be used to triage sicker patients more quickly to an ICU bed before later signs such as the development of lactic acidosis and organ dysfunction develop, but also could potentially identify patients at risk for undertreated infections and complications who could benefit from further interventions such as escalation of antibiotics, renewed search for occult infection, and possible surgical interventions and

other methods of source control. Several studies have examined the relationship between PCT and mortality related to sepsis.

In a multicenter study of ICUs across Greece, the Hellenic Sepsis Study Group found that 28-day mortality rates for ICU patients with admit PCT levels ≤ 0.85 ng/mL were 25.6% compared to 45.3% for patients with levels > 0.85 ng/mL (odds ratio, 2.404; 95% CI, 1.385-4.171; $P < 0.0001$).[10] In a follow-up study by the same group examining the effect of early changes in PCT levels, a decrease in PCT levels by > 30% or a level < 0.25 ng/mL by 72 hours after admission was associated with improved 28-day survival and was an independent indicator of favorable outcome regardless of disease severity.[11]

Other observational studies have also reported that changes in PCT rather than absolute values correlate with patient mortality. In a Finnish sepsis study, hospital mortality for patients admitted with sepsis was 12.2% in the group whose PCT decreased by at least 50% within 72 hours compared to 29.8% for patients with a < 50% decrease in PCT ($P = 0.007$).[12] In a similar vein, a more recent U.S. study found that a PCT decrease of 80% over 72 hours was associated with a negative predictive value of 90% (95% CI, 0.77-0.97) for both ICU and hospital mortality.[13] Extending this idea further, a larger German cohort study of 472 patients admitted to the ICU (including non-septic patients) found that an increase in the PCT level the first day after reaching a threshold of ≥ 1.0 ng/mL was independently associated with a 1.8-fold increased risk of mortality at 90 days (95% CI, 1.3-2.7; $P = 0.002$), with sustained increases over day 2 and 3 associated with progressively higher risks of mortality (relative risk [RR], 2.2; 95% CI, 1.6-3.0; $P < 0.0001$ and RR, 2.8; 95% CI, 2.0-3.8; $P < 0.0001$, respectively).[14]

Despite these findings, however, the only interventional study done thus far based on PCT levels failed to show an improvement in patient outcomes. The Procalcitonin and Survival Study (PASS) was a multicenter, randomized, controlled trial where patients were randomized to either a standard care or PCT group. In the PCT group, antimicrobial interventions were guided by "alert" or "nonalert" values. "Alert procalcitonin" was defined as a PCT level ≥ 1.0 ng/mL that was not decreasing by at least 10% from the previous day; if present, it prompted the medical team to increase substantially their antimicrobial spectrum coverage and to intensify efforts to find occult/uncontrolled sources of infection per protocol. Not only was 28-day mortality — the primary outcome — similar between the two groups, the PCT group had a higher number of days on mechanical ventilation (absolute difference 4.9%, $P < 0.0001$), longer ICU stays by 1 day ($P = 0.004$), and more evidence of acute kidney injury.[15] The authors hypothesized that the increased antibiotic exposure in the PCT intervention group may have induced prolonged organ failure in this group.

PROCALCITONIN TO GUIDE ANTIBIOTIC DECISIONS IN SEPSIS

There has been considerable interest in promoting antibiotic stewardship in efforts to decrease the emergence of multidrug-resistant organisms and complications such as *Clostridium difficile* infection. Only five randomized, controlled trials have evaluated whether the use of PCT algorithms results in reduced antibiotic exposure without a harmful effect on patient outcomes in patients with sepsis. Two were performed specifically in the postoperative setting and found reductions in antibiotic exposure of 20% and 25% without differences in mortality, although neither was adequately powered to determine non-inferiority.[16,17] The most recent trial by Annane et al was performed in a subset of patients with severe sepsis without a clear source of infection; their findings did not show evidence of a significant difference in antibiotic exposure with use of a PCT algorithm, although the study was terminated early due to low incidence of patients meeting their criteria.[18]

In a single-center study, Nobre et al found that duration of antibiotics was shorter by 3.2 days (95% CI, 1.1-5.4; $P = 0.003$) with no significant difference in 28-day and ICU mortality, and similar rates of cure in the PCT group.[19] These findings, however, were observed only after using a per-protocol analysis that excluded a higher number of patients in the PCT group due to death, transfer, or the presence of complicated infections requiring extended antibiotics rather than an intention-to-treat analysis. Although the authors argue that this was their *a priori* target population, their final numbers were too small to conclude definitively that a shortened antibiotic course based on PCT levels did not do any harm.

The PRORATA trial, which included 630 patients in multiple ICUs in France, is the only study sufficiently powered to determine non-inferiority in terms of 28-day and 60-day mortality between a PCT-guided antibiotic management protocol and standard care. The

Table. PCT-based Antibiotic Algorithm				
Initiating antibiotics*				
PCT threshold	< 0.25 μg/L	0.25 to < 0.5 μg/L	0.5 to < 1 μg/L	≥ 1 μg/L
Recommendation	Antibiotics strongly discouraged	Antibiotics discouraged	Antibiotics encouraged	Antibiotics strongly encouraged
During antibiotic therapy				
PCT threshold	< 0.25 μg/L	Decrease by ≥ 80% from peak, or 0.25 to < 0.5 μg/L	Decrease by < 80% from peak, and ≥ 0.5 μg/L	Increase compared to peak and ≥ 0.5 μg/L
Recommendation	Stopping antibiotics strongly encouraged	Stopping antibiotics encouraged	Continuing antibiotics encouraged	Changing antibiotics strongly encouraged
*If PCT level drawn early in episode, obtain a second level 6-12 hours later Adapted from Bouadma L, et al.[8]				

authors found that patients in the PCT group had 2.7 more antibiotic-free days (95% CI, 1.4-4.1; $P < 0.0001$) and a 23% relative reduction in days of antibiotic exposure, without a significant difference in overall mortality at 28 and 60 days.[8] In addition, there were no significant differences in many secondary outcomes, including rate of relapse, superinfection, emerging multidrug-resistant bacteria, and ICU and hospital length of stay. The PCT-based antibiotic algorithm they used is summarized in the Table.

CONCLUSION

PCT has garnered significant interest as a biomarker in the management of critically ill patients with sepsis based on a number of studies mostly done in Europe. Currently, the FDA has approved at least three quantitative PCT assays in the United States that are commercially available, each costing an average of $25-30 per assay with turnaround time ranging from 1 hour to 1 day.[20] Based on currently available data, the role of PCT as a diagnostic tool for sepsis appears limited given that its testing characteristics, especially negative predictive value, are insufficient to stop clinicians from superseding PCT protocols in favor of clinical judgment in this high-stakes population. Although there are multiple studies reporting that changes in PCT level correlate with mortality in patients with sepsis, the only interventional trial performed thus far has not shown that escalation of therapy based on PCT values has been beneficial, but has shown it actually may cause harm. Perhaps the most meaningful use of PCT may be in helping to determine the duration of antibiotic therapy in situations where an extended course of antibiotics is not necessarily required. There appears to be no worsening of patient mortality, but future studies should also focus on rate of recurrent infections and other infection-related complications as primary outcomes as well as the overall cost-effectiveness of this approach. ■

REFERENCES

1. Martin GS, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546-1554.

2. Dellinger RP, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.

3. Uzzan B, et al. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis. *Crit Care Med* 2006;34:1996-2003.

4. Tang BM, et al. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: Systematic review and meta-analysis. *Lancet Infect Dis* 2007;7:210-217.

5. Wacker C, et al. Procalcitonin as a diagnostic marker for sepsis: A systematic review and meta-analysis. *Lancet Infect Dis* 2013; 13:426-435.

6. Jekarl DW, et al. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. *Diagn Microbiol Infect Dis* 2013; 75:342-347.

7. Llewelyn MJ, et al. Sepsis biomarkers in unselected patients on admission to intensive or high-dependency care. *Crit Care* 2013; 17:R60.

8. Bouadma L, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomized controlled trial. *Lancet* 2010;375:463-474.

9. Layios N, et al. Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. *Crit Care Med* 2012;40:2304-2309.

10. Giamarellos-Bourboulis EJ, et al. Procalcitonin as an early indicator of outcome in sepsis: A prospective observational study. *J Hosp Infect* 2011;77:58-63.

11. Georgopoulou AP, et al. Early changes of procalcitonin may advise about prognosis and appropriateness of antimicrobial therapy in sepsis. *J Crit Care* 2011;26:331e1-7.

12. Karlsson S, et al. Predictive value of procalcitonin decrease in patients with severe sepsis: A prospective observational study. *Crit Care* 2010;14:R205.

13. Schuetz P, et al. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. *Crit Care* 2013;17:R115.

14. Jensen JU, et al. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med* 2006;34:2596-2602.

15. Jensen JU, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial. *Crit Care Med* 2011;39:2048-2058.

16. Hochreiter M, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: A randomized prospective controlled trial. *Crit Care* 2009;13:R83.

17. Schroeder S, et al. Procalcitonin (PCT) – guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: Results of a prospective randomized study. *Langenbecks Arch Surg* 2009;394:221-226.

18. Annane D, et al. Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: A randomized controlled trial. *BMJ Open* 2013;3:e002186.

19. Nobre V, et al. Use of procalcitonin to shorten antibiotic treatment duration in septic patients. *Am J Respir Crit Care Med* 2008;177:498-505.

20. Schuetz P, et al. Role of procalcitonin in managing adult patients with respiratory tract infections. *Chest* 2012;141:1063-1073.

ABSTRACT & COMMENTARY

Can Integrating the Critical-Care Pain Observation Tool into Practice Improve Pain Management?

By Linda L. Chlan, RN, PhD

Dean's Distinguished Professor of Symptom Management Research, The Ohio State University, College of Nursing

Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

SYNOPSIS: Using the Critical-Care Pain Observation Tool to routinely assess pain in non-verbal ICU patients improved both the frequency of documented pain assessments and the administration of analgesics in two Canadian ICUs.

SOURCE: Rose L, et al. Behavioral pain assessment tool for critically ill adults unable to self-report pain. *Am J Crit Care* 2013;22:246-255.

Critically ill patients experience pain from a variety of procedures and/or have underlying medical conditions that exacerbate pain levels. Further, non-verbal patients receiving mechanical ventilation recall experiencing pain while in the ICU. Despite clinicians' best efforts, patients still experience pain, and the challenge of assessing pain in non-responsive or non-verbal patients remains. One instrument that uses behavioral responses associated with pain is the Critical-Care Pain Observation Tool (CPOT). The CPOT consists of four domains: facial expression, body movement, muscle tension, and compliance with the ventilator or vocalization for non-intubated patients. Each domain is scored 0-2; the maximum score is 8 with higher scores indicative of pain. Unfortunately, simple tools such as the CPOT are not routinely used to assess pain in the ICU. Thus, the authors of this paper aimed to determine the effects of instituting the CPOT for routine pain management on the frequency of pain assessments documented and the influence on analgesia and sedation administration in non-verbal ICU patients.

This before-and-after designed study was conducted in a 600-bed hospital in Toronto. Patients and staff on a 20-bed medical-surgical-trauma unit (MSTU) and a 14-bed cardiovascular ICU (CVICU) participated in the study. A 4-month baseline/before phase consisted of educational sessions with unit protocols and flow sheets modified to incorporate the CPOT. In addition, one-on-one beside nurse education was also provided. To reduce any bias, data were abstracted retrospectively from any patient chart that met the inclusion criteria of inability to communicate verbally or a motor score of ≤ 5 on the Glasgow Coma Scale. A total of 524 pain assessment intervals (PAIs), or frequency of pain assessments, were completed before implementation of the CPOT on 189 individual patients, and 524 in the after phase with 184 individual patients. Data were also abstracted from the medical record on patient demographic characteristics and doses of analgesic and sedative medications. Audits for adherence to the desired every-4-hour pain assessment documentation were obtained retrospectively from the medical record and incorporated into individual staff nurse performance reviews.

Patient characteristics in age, gender, and illness severity were similar in the before- and

after-study phases. The proportion of PAIs in the CVICU increased from 15% in the before phase to 64% in the after phase. Likewise, the MSTU saw an increase in PAIs from 22% to 80%. Neither unit ever achieved the target goal of 100% PAIs. Medication administration practices also changed after implementation of the CPOT on the participating ICUs. The CVICU reported a significant decrease in opioid administration, while the MSTU saw an increase. Administration of benzodiazepines decreased in the CVICU but was unchanged in the MSTU. There was no difference in length of mechanical ventilation after CPOT implementation in either ICU. While overall opioid administration improved on both ICUs, the authors reported that 40% of PAIs with CPOT scores indicating a need for analgesia were not followed up with opioid administration. The authors concluded that further work is needed to link pain assessment findings to actual pain management strategies.

■ COMMENTARY

The management of pain and other distressful symptoms in critically ill patients unable to verbalize the intensity of these symptoms remains an immense challenge for the critical care clinician. Further, in order to palliate symptoms such as pain with appropriate administration of analgesic medications, some idea of the intensity of pain is required. This paper by Rose and colleagues documents the implementation of one behavioral pain assessment tool, the CPOT, on two Canadian ICUs using a before-and-after design. While this design is not as powerful as a randomized clinical trial, several important points are advanced by the study's findings. Despite the best efforts of the research team, 100% attainment of pain documentations was never achieved. These efforts included pain assessment practice adherence to standards in annual performance reviews. The highest rate achieved was an 80% adherence rate to documentation of pain assessments. A surprising finding was that a full 40% of CPOT assessments indicated the need for analgesia administration, but this was not carried out. This indicates the need for further practice change initiatives aimed at improving pain management practices.

While the challenge remains to effectively manage symptoms in non-verbal ICU patients, the CPOT may be one instrument that can improve pain management practices. ■

ABSTRACT & COMMENTARY

Safety of Intrahospital Transport Among Ventilated Critically Ill Patients

By Eric C. Walter, MD, MSc

Pulmonary and Critical Care Medicine, Northwest Permanente and Kaiser Sunnyside Medical Center, Portland

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

SYNOPSIS: In this prospective, multicenter cohort study, intrahospital transport of ventilated patients was common and associated with complications. Whether these complications are directly attributable to the transport is questionable.

SOURCE: Schwebel C, et al. Safety of intrahospital transport in ventilated critically ill patients: A multicenter cohort study. *Crit Care Med* 2013; 41:1919-1928.

The transport of any patient within a hospital involves removing them from their care setting. When patients are critically ill and ventilated, the challenges and potential risks of transport are magnified. This paper used a very large, multicenter, prospective cohort of more than 6000 ventilated critically ill patients in France to better understand the risks associated with intrahospital transport (excluding transport to the operating room).

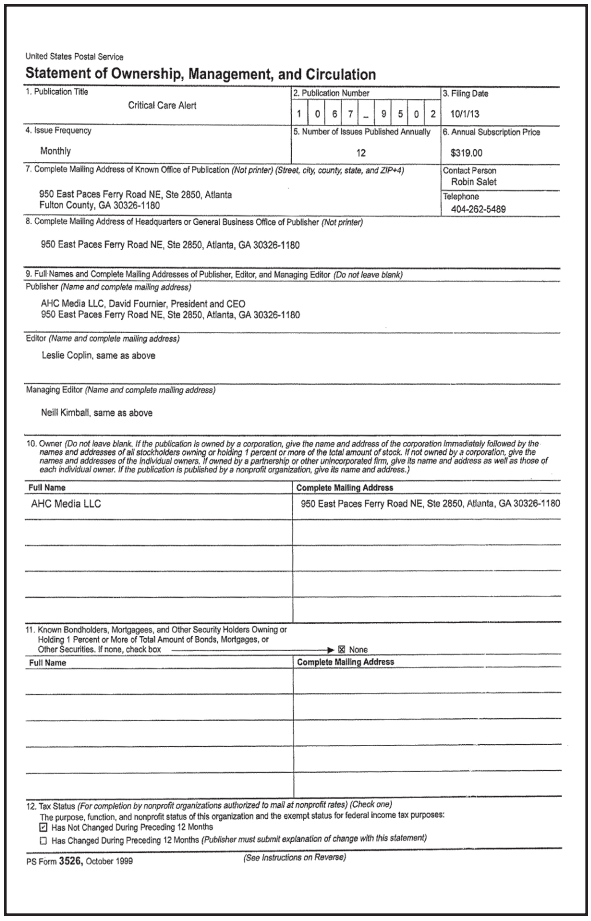
Intrahospital transport was common; 28.6% of patients experienced one or more transports. The vast majority of transports were to the CT scanner (93.6%). Patients who were transported were sicker than patients who never required transports. They were more likely to be sedated (79% vs 43%), to be on vasopressor support (53% vs 47%), and had a higher Simplified Acute Physiology Score II (50 vs 45). They were also more likely to be on parenteral support (53% vs 47%) and have arterial (54% vs 41%) or central catheters (64% vs 51%).

Because of the differences in severity of illness, the authors developed a propensity score for transport in order to try to identify complications of transport. A propensity score was calculated by identifying factors associated with transport. These factors were then used to generate a score that estimated the propensity of transport. This score was then applied to both patients who were and were never transported in an effort to match patients and control for both measured and unmeasured confounders. After controlling for the propensity for transport, the ICU length of stay was longer among transported patients than never transported patients (7 vs 3 days). A long list of complications occurred more often in transported patients, including severe bleeding, deep vein thrombosis, pneumothorax, ventilator-associated pneumonia, atelectasis, hypoglycemia, and hyperglycemia. Interestingly, despite the increased complications, there was a trend toward decreased mortality among patients who were transported (28% vs 35%).

■ COMMENTARY

Schwebel and colleagues should be commended for their attempt to understand such a common but difficult topic to study. Intuitively, it makes sense that intrahospital transfers of ventilated patients might place patients at risk for complications. The authors conclude that their data prove this. I think this conclusion is overstated. It is hard to understand how a trip to the CT scanner could cause deep venous thrombosis or hypernatremia. The data strongly suggest that patients who were transported were sicker than those who were not transported. It is more likely that the sickest patients required more transports out of the ICU for procedures or imaging and that the severity of illness in this population accounted for many of the observed complications. The authors appropriately attempted to control for this bias by calculating a propensity score. However, I am not convinced that the propensity score was enough to account for all unmeasured confounders in this study.

It would be unwise to fully dismiss this study. Transports are risky times for ventilated ICU patients but are often not given much thought. While this study does not prove that intrahospital transports of ventilated patients lead to more complications, it also does not prove a lack of complications. ■



United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
Critical Care Alert	1 0 6 7 _ 9 5 0 2	10/1/13
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)*
950 East Paces Ferry Road NE, Ste 2850, Atlanta
Fulton County, GA 30326-1180
Contact Person: Robin Sallet
Telephone: 404-262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*
AHC Media LLC, David Fournier, President and CEO
950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

Editor *(Name and complete mailing address)*
Leslie Coplin, same as above

Managing Editor *(Name and complete mailing address)*
Neill Kimball, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

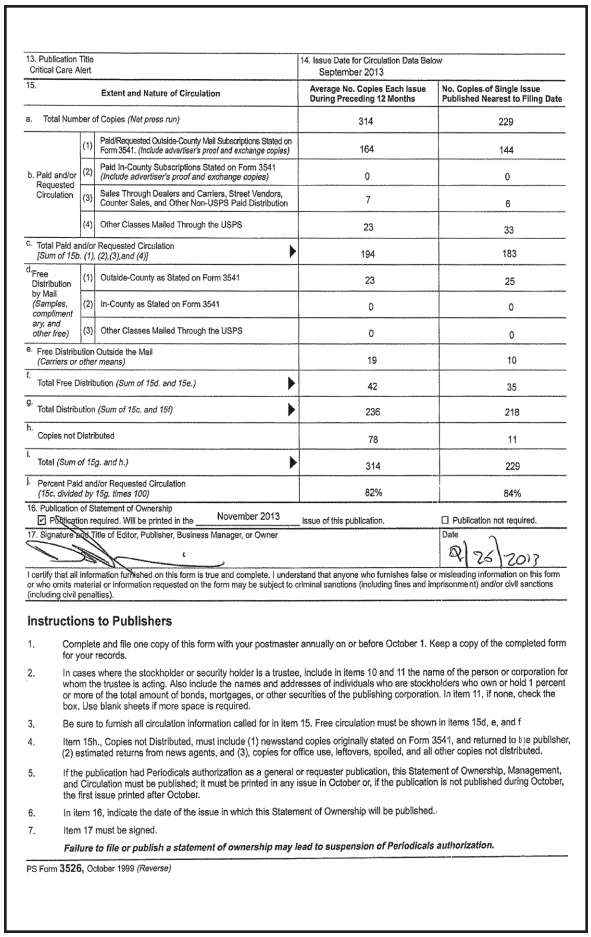
Full Name	Complete Mailing Address
AHC Media LLC	950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☒ None

Full Name	Complete Mailing Address

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, October 1999 *(See Instructions on Reverse)*



13. Publication Title: Critical Care Alert	14. Issue Date for Circulation Data Below: September 2013	
15. Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies *(Net press run)*	314	229
b. Paid and/or Requested Circulation (1) Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	164	144
(2) Paid In-County Subscriptions Stated on Form 3541 *(Include advertiser's proof and exchange copies)*	0	0
(3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	7	6
(4) Other Classes Mailed Through the USPS	23	33
c. Total Paid and/or Requested Circulation *[Sum of 15b. (1), (2),(3),and (4)]*	194	183
d. Free Distribution by Mail *(Samples, complimentary, and other free)* (1) Outside-County as Stated on Form 3541	23	25
(2) In-County as Stated on Form 3541	0	0
(3) Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or other means)*	19	10
f. Total Free Distribution *(Sum of 15d. and 15e.)*	42	35
g. Total Distribution *(Sum of 15c. and 15f)*	236	218
h. Copies not Distributed	78	11
i. Total *(Sum of 15g. and h.)*	314	229
j. Percent Paid and/or Requested Circulation *(15c. divided by 15g. times 100)*	82%	84%

16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2013 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner — Date: 9/26/2013

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or, if the publication is not published during October, the first issue printed after October.
6. In item 16, indicate the date of the issue in which this Statement of Ownership will be published.
7. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of Periodicals authorization.

PS Form **3526**, October 1999 *(Reverse)*

CME/CNE Questions

1. Which of the following statements is true regarding the use of procalcitonin in the diagnosis of sepsis?

a. It is been shown to be better than clinical judgment.
b. Very low levels (< 0.25 ng/mL) should be sufficient to inform the clinician to withhold antibiotics given sepsis is highly unlikely.
c. It has high sensitivity, but poor specificity.
d. It is the gold standard for diagnosing sepsis.
e. None of the above

2. In the PRORATA trial, the use of a procalcitonin-guided antibiotic treatment algorithm resulted in:

a. decreased exposure to antibiotics.
b. no difference in 28-day or 60-day mortality compared to standard care.
c. increased infection relapse rate with a multidrug-resistant organism.
d. All of the above
e. Only a and b

3. Which of the following dimensions are measured by the Critical-Care Pain Observation Tool (CPOT)?

a. Response to painful stimuli, muscle force, verbal commands
b. Facial expressions, body movement, muscle tension, vocalization/compliance with the ventilator
c. Compliance with the ventilator, response to verbal stimuli, purposeful body movements
d. Orientation to person, place, time, and response to verbal stimuli
e. None of the above

4. Which of the following statements best summarizes the main findings of the study by Rose and colleagues?

a. Patients received longer periods of mechanical ventilatory support after integrating the CPOT into ICU practice.
b. An overall adherence rate of 100% to pain assessment intervals was achieved in the after phase of the study.
c. The number of documented pain assessments increased significantly in both participating ICUs.
d. The nurses in the CVICU were against using the CPOT in their routine patient-care practices.
e. All of the above

5. Ventilated patients who had intrahospital transports:

a. were sicker than patients who were never transported.
b. were most frequently transported for chest x-rays.
c. had an increased mortality compared to patients who were never transported.
d. had a shorter ICU stay than patients who were never transported.
e. required less vasopressor support than patients who were never transported.

6. The propensity score:

a. eliminates bias from unmeasured confounders in observational studies.
b. was calculated by identifying variables associated with the need for ventilation in this study.
c. was calculated in order to assess how often patients were transported.
d. was used to measure the time out of the ICU during transports.
e. was used to match patients who were transported with patients who were never transported in an attempt to control for both measured and unmeasured confounders in this study.

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.

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

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

VOLUME 18, NUMBER 11 PAGES 21-22 NOVEMBER 2013

Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media, LLC.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

AHC Media

Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

Clinical Briefs in Primary Care is going digital!

Beginning with the January issue, *Clinical Briefs in Primary Care* can be found exclusively online. It will no longer be inserted in your newsletter. You will find the same high-quality, evidence-based updates in primary care that you know and trust. You will be able to access the online edition anywhere. We hope this transition will better meet your needs as a subscriber. Stay tuned for more information about this digital transition. We will keep you posted on all the details!

Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

Pharmacology Watch is going digital!

Beginning with the January issue, *Pharmacology Watch* can be found exclusively online. It will no longer be inserted in your newsletter. You will find the same high-quality, evidence-based updates in clinical pharmacology that you know and trust. You will be able to access the online edition anywhere. We hope this transition will better meet your needs as a subscriber. Stay tuned for more information about this digital transition. We will keep you posted on all the details!