EVIDENCE-BASED INFORMATION FOR HOSPITALISTS, INTENSIVISTS, AND ACUTE CARE CLINICIANS

HOSPITAL MEDICINE ALERT

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Upon Further Review: Femoral Venous Catheters Do Not Increase Risk of Catheter-Related Bloodstream Infection

ABSTRACT & COMMENTARY

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH

Dr. Watkins reports no financial relationships in this field of study.
This article originally appeared in the January 2013 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

Synopsis: *In a meta-analysis, investigators found that recent studies show no difference in the risk of catheter-related bloodstream infections between internal jugular, subclavian, and femoral sites. Older studies had a lower risk for the internal jugular site compared to the femoral site.*

Source: Marik PE, et al. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: A systemic review of the literature and meta-analysis. *Crit Care Med* 2012;40(8):2479-85.

Volume 7 • Number 12 • February 2013 • Pages 89-96

NOW AVAILABLE ONLINE
WWW.AHCMEDIA.COM

Financial Disclosure:

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, executive editor Russ Underwood, and associate managing editor Jill Drachenberg have no relevant financial relationship related to the material presented in this issue.

Catheter-related bloodstream infections (CRBSIs) cause significant morbidity and mortality. They are also very costly, approximately $50,000 per infection, for which hospitals are not reimbursed by Medicare and Medicaid. It is widely believed that the femoral site is less safe in terms of infection risk compared to the subclavian (SC) and internal jugular (IJ) sites. Indeed, guidelines from the CDC and IDSA on preventing CRBSIs advise against using the femoral vein for central access.[1,2] In order to evaluate the evidence behind this recommendation, Marik and colleagues performed a systematic review and meta-analysis comparing the risk in adults for CRBSIs for catheters placed in the femoral vs. internal jugular and subclavian sites.

The authors identified studies published between 1966 to October 2011 that reported the rate of CRBSI at the femoral, SC and/or IJ sites. They sub-grouped according to study design and assessed heterogeneity and bias. Two randomized controlled trials and eight cohort studies were included in the meta-analysis. There was no significant difference in risk for CRBSI between the femoral and SC sites (RR 1.75, 95% CI 0.80-3.8, P = .16). Meta-regression showed a significant interaction between the risk of infection and year of study publication, where earlier studies favored the SC site (P = .05). Overall, the IJ site was associated with a significantly reduced risk for CRBSI compared to the femoral site (RR 1.90, 95% CI 1.21-2.97, P = .005). However, when two outlier studies were removed from the analysis there was no significant difference between the femoral and IJ sites (RR 1.35, 95% CI 0.84-2.10, P = .2). Meta-regression again demonstrated a significant interaction between year of publication and risk for infection, with earlier studies favoring the IJ site (P = .01). There was no significant difference in CRBSI rate between the SC and IJ sites (RR 1.09, 95% CI 0.67-1.75, P = .74). Finally, there was no difference in risk for deep vein thrombosis (DVT) between the femoral site and the IJ and SC sites combined. Significant heterogeneity was found between the studies.

■ COMMENTARY

Conventional wisdom teaches that the SC vein is superior to the IJ for preventing CRBSIs, which in turn is superior to the femoral vein. The findings of the present study i.e. recent data show no difference in risk of CRBSIs between the femoral, IJ and SC sites, challenge this belief as well as current guideline recommendations about avoiding the femoral site. Moreover, a recent Cochrane review also found no difference in CRBSI rate among the three insertion sites.[3] Except for certain patients for whom the femoral site should be avoided (obese, renal transplant recipients, on chronic hemodialysis), Marik and colleagues recommend that insertion sites be chosen based on the lowest likelihood of injury.

This study does have several limitations. First, one of the RCTs was conducted before the line-bundle standard was implemented and the other did not include patients with a body mass index greater than 45. It seems intuitive that changes in line insertion techniques in recent years, such as improved hand hygiene, use of chlorhexidine for skin decontamination, full-body drapes, catheter-insertion checklists, and ultrasound guidance for placement are a major cause for declines in CRBSI rates. Second, they did not distinguish between CRBSI and catheter colonization rate, as not all colonized catheters necessarily equal clinical infection. Third, the authors used data that combined outcomes for standard and antimicrobial catheters. Finally, the incidence of DVT may have declined over time due to heparin usage as part of the ventilator bundle.

Is it time to abandon the axiom about avoiding femoral central lines? Probably not yet, although the practice does seem safer now than in the past. As Marik and colleagues acknowledge, the rate of CRBSIs in the U.S. has declined from 5.32/1,000 catheter days in 1998 to 2.05/1000 catheter days in 2009. It is possible that this is due in part to clinicians not using the femoral site, but

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305. Website: www.ahcmedia.com.

EXECUTIVE EDITOR: Russ Underwood.
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Hospital Medicine Alert,* P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: russ.underwood@ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $249
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

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.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

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 *20 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for hospitalists, intensivists, and acute care clinicians. It is in effect for 36 months from the date of the publication..

Questions & Comments
Please call Russ Underwood, Executive Editor, at (404) 262-5521 or e-mail at russ.underwood@ahcmedia.com.

more likely it is from better catheter insertion practices. However, it may be time to re-examine current guideline recommendations and at least acknowledge that the femoral site might be an option, with the caveat that the final decision about site placement requires a careful analysis of the risks and benefits. ■

References

1. O'Grady NP, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011;52:e162-93.
2. Marschall J, et al. Strategies to prevent central-line associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008;29(Suppl1):S22-S30.
3. Ge X, et al. Central venous access sites for the prevention of venous thrombosis, stenosis and infection. *Cochrane Database Syst Rev* 2012;3:CD004084.

Risk of Angioedema with Drug Therapy

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

This article originally appeared in the January 2013 issue of Clinical Cardiology Alert. *It was peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

Source: Toh S, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012;172:1582-1589.

Angioedema is an infrequent, but serious, adverse event from drug therapy. Drugs that affect the renin-angiotensin-aldosterone system have been linked to angioedema, but the relative frequency of this complication with these drugs is poorly understood. Thus, this group of investigators used the FDA's Mini-Sentinel Distribution Database (MSDD) to explore this issue. The MSDD is a pilot program involving 17 health plans for an eventual national system for monitoring the safety of medical products. An inception cohort design was used to assess patients > 18 years old receiving only an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), aliskiren, or a beta-blocker (reference group). The primary endpoint was a new diagnosis of angioedema and the secondary outcome was serious angioedema (airway obstruction requiring in-patient care). The study was censured if angioedema occurred, the drug was stopped, another drug in this group was started, or 1 year had passed. There were approximately 1.8 million initiated on ACEIs, 467,000 on ARBs, 4867 on aliskiren, and 1.6 million on beta-blockers. Mean follow-up for ACEIs was 149 days, ARBs 136 days, aliskiren 112 days, and beta-blockers 126 days. Among the approximately 4 million patients studied, there were 4511 cases of angioedema and 388 cases of serious angioedema. The incidences per 1000 persons were 1.79 for ACEIs, 0.62 for ARBs, 1.44 for aliskiren, and 0.58 for beta-blockers. Serious angioedema rates were 0.18 for ACEIs, 0.02 for ARBs, 0.21 for aliskiren, and 0.03 for beta-blockers. The authors concluded that compared to beta-blockers, the risk of angioedema is highest with ACEIs or aliskiren and lowest with ARBs.

■ COMMENTARY

This large, well-done retrospective, observational study has important implications for the care of patients. Angioedema and serious angioedema in patients receiving drugs that have been associated with angioedema is rare. Even patients receiving drugs not thought to be associated with angioedema (beta-blockers) have a measurable risk of angioedema. In fact, in this study, the incidence of serious angioedema was higher with beta-blockers than ARBs. The main result of this study is that compared to beta-blockers, ACEIs and aliskiren have a three-fold higher incidence of angioedema and ARBs are 16% higher. Serious angioedema is five times more common with ACEIs vs. beta-blockers. This is a robust study involving about 4 million patients among whom over 50% were women. One limitation of this study is a lack of racial or ethnicity data; African Americans are known to have a higher incidence of angioedema. However, this study did confirm that women and those > age 65 years have higher rates of angioedema with ACEIs, but not ARBs. So, my question at this time is: Is there any reason to use ACEIs vs ARBs, especially in outpatients with hypertension facing decades of therapy? I think not, especially since at least one ARB is now generic. ■

Rapid Response Teams: Evidence of a Broader Impact that Influences Morale and Nursing Workload

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, RN, PhD

Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

Leslie A. Hoffman reports no financial relationships relevant to this field of study. This article originally appeared in the January 2013 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

Synopsis: *Advantages of a rapid response team extended beyond a reduction in codes to impact multiple endpoints, including positive effects on nurse morale and empowerment, unit workload, and education.*

Source: Benin AL, et al. Defining impact of a rapid response team: Qualitative study with nurses, physicians and hospital administrators. *BMJ Qual Saf* 2012;21:391-398.

In this study, the authors sought to elicit perceptions of the impact of a rapid response team (RRT) by interviewing care providers. The study was conducted at the Yale New Haven Hospital where the RRT covered 43 patient care units. The team was comprised of a rotating hospitalist physician, critical care nurse, and respiratory therapist. Those interviewed included 49 participants (16 physicians, 22 nurses, eight administrators, and three respiratory therapists). Nurses viewed the RRT as providing a sense of security and empowerment, resulting from knowing they could summon help immediately. As noted by one nurse, "It's very comforting to have someone who can help assess the patient, determine if they are too sick to remain on the unit, and support us." Nurses valued being able to call the RRT if "something did not seem right," even if ill defined. Hospitalists had divergent opinions: Some valued the opportunity to keep skills current through exposure to an unstable, decompensating patient, whereas others found the need to respond to calls "extremely disruptive" and a "huge stressor" that diverted time and attention from their caseload. One benefit was unexpected: Housestaff and nurses valued RRT calls as a means to realign their workload and give more attention to other assigned patients. As one nurse noted, "I'm focusing on one patient and hurting four other patients. I called in another nurse and now her four patients are also not seeing the care they need." Administrators viewed the RRT as a means to appropriately triage patients to the ICU, as well as a means to avert ICU transfers when appropriate, and to play an important role in nurse retention and improving nurse morale.

■ **COMMENTARY**

RRTs were introduced to provide a hospital-wide mechanism for bringing critical care expertise to patients who developed unexpected, potentially life-threatening clinical deterioration. Although initial studies showed a beneficial effect, subsequent studies failed to confirm these findings, leading to questions about the need for this resource. In these studies, "outcome" was typically evaluated by pre/post cardiac arrest and mortality data. Findings of this study suggest more subtle benefits that translate to all patients on the clinical unit where the call is placed. Nurses valued the ability to summon a highly experienced team, allowing the team to manage the unstable patient and thus redirect attention to other assigned patients they had neglected. Housestaff mentioned the same advantage, particularly on nights and weekends when faced with multiple admissions plus a highly unstable patient who required 1:1 attention. Administrators supported positive views, citing the RRT as a means to improve patient flow and nurse retention. There were also negative opinions that cited workload disruption, potential negative impact on housestaff education, and conflicts regarding how care should be provided. Findings of this study support the need to evaluate the impact of RRT in ways that extend beyond codes and mortality. ■

Threshold Vital Sign Abnormalities as Triggers for Rapid Response Activation

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle

This article originally appeared in the January 2013 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD. Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

Synopsis: *This study shows that as hospitals adopt electronic workflows, automatic triggering of a rapid response system based solely on changes in vital signs could place a tremendous burden on the system.*

Source: Fagan K, et al. Vital sign abnormalities, rapid response, and adverse outcomes in hospitalized patients. *Am J Med Qual* 2012; Feb 28. [Epub ahead of print.]

Fagan and colleagues at Denver Health Medical Center examined electronic data collected on all adult patients who generated a medical surgical acute-care room charge during a recent 6-month period and remained on the ward for at least 24 hours. At the authors' institution, all vital signs are entered into an electronic database. Rapid-response activation (RRA) occurs whenever any of the following threshold vital sign abnormalities (TVSAs) is entered: respiratory rate < 8 or > 28 breaths/min, heart rate < 50 or > 120 beats/min, systolic blood pressure < 90 mmHg, diastolic blood pressure > 110 mmHg, oxygen saturation by pulse oximetry < 90% despite supplemental oxygen, or temperature > 39° C. The investigators examined data from patients for whom an RRA occurred, comparing them to non-RRA patients who had at least one TVSA and also to patients in whom neither of these occurred. Outcomes sought were in-hospital mortality, non-ICU cardiopulmonary arrest, and unexpected ICU transfer.

During the study period, there were 9074 adult patient discharges. A total of 2018 of these were non-index hospitalizations for those patients (only the first admission for a given patient during the study interval was used), and 728 admissions were for less than 24 hours. An additional 2485 admissions did not generate a medical-surgical acute-care room charge, leaving 3843 hospitalizations (22,126 acute-care hospital days; 545,773 electronically documented vital signs) that constituted the study population. RRA occurred in 120 patients (3.1%), of whom 114 (95%) had a TVSA. An additional 1111 patients (29%) had at least one TVSA but no RRA, and 2612 patients (68%) had neither of these.

Patients for whom an RRA occurred were more likely to be female and have longer hospital lengths of stay than patients without an RRA. They were more likely to be transferred unexpectedly to the ICU (20.8% vs. 7.3% for patients with TVSA but no RRA, and 1.7% for patients with neither; $P < 0.01$), and had a non-significant trend toward being more likely to experience a cardiopulmonary arrest during the hospitalization (1.7% vs. 0.2% vs. 0.3%, respectively; $P = 0.07$). Patients for whom an RRA occurred were more likely to have one or more of the sought-after adverse events than patients in either of the other groups. However, only 2.5% of TVSA recorded during the hospitalization triggered an RRA (120 RRAs for 4739 TVSAs), with a low systolic blood pressure and an elevated heart rate being the first and second most common TVSAs. Overall, one of every 20 recorded vital sign episodes contained a TVSA by the institution's threshold criteria, and about the same proportion of patient-days included at least two TVSAs in a single day.

Considering the entire patient population, the sensitivity of any TVSA for predicting an adverse event during hospitalization was 70%. However, the occurrence of any TVSA was the least specific of all characteristics examined (70%), with a positive predictive value (PPV) of only 9.2%. Four of the individual vital sign thresholds had PPVs < 10%, while an elevated respiratory rate had the highest PPV at 46%. The fact that only 120 RRAs were called, in the face of 4739 TVSAs that occurred during the same period, supports the assumption that the floor nurses exercised judgment and used additional clinical information in deciding whether the TVSA should trigger an RRA. The authors point out that if their institution were to automate the activation of their rapid response system based on their current thresholds, "we would immediately overwhelm our current resources to respond."

■ COMMENTARY

Although it is hard to argue with the concept that identifying, assessing, and intervening with non-ICU patients who experience acute clinical deterioration should improve both clinical and administrative outcomes, demonstration of this assumed benefit and the establishment of the right triggering mechanisms for rapid response have proven to be challenging. This study shows that electronically detecting vital sign changes by themselves is not the answer in terms of system efficiency and personnel costs. Ward patients whose vital signs were never recorded in the abnormal range that would qualify for a TVSA had an exceedingly low rate of adverse events. However, this study also demonstrates that if generally accepted vital sign abnormalities were used as the only criteria for triggering a rapid response system, the great majority of such calls would be false alarms and the logistics of responding to them all would be prohibitive. As hospitals

become more reliant on electronic databases and automate more of their operations, the crucial importance of the bedside nurse's clinical skills in the operation of a rapid response system must not be left out of the equation. ■

Steroids for Bacterial Meningitis: Long-term Follow-up

ABSTRACT & COMMENTARY

By Joseph Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Safdieh reports no financial relationships relevant to this field of study. This article originally appeared in the January 2013 issue of Neurology Alert. *It was edited by Matthew E. Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital, and Dr. Beal is Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Fink is a retained consultant for MAQUET, and Dr. Beal reports no financial relationships relevant to this field of study.*

Synopsis: *Use of dexamethasone in community-acquired bacterial meningitis is associated with long-term survival in treated patients.*

Source: Fritz D, et al. Dexamethasone and long-term survival in bacterial meningitis. *Neurology* 2012;79:2177-2179.

Bacterial meningitis is a serious, often life-threatening, condition. Patients generally present with acute onset of fever, headache, and nuchal rigidity, and often have associated photophobia, nausea, and altered mental status. The diagnosis can be made quickly with lumbar puncture and patients clearly benefit from early initiation of appropriate intravenous antimicrobial therapy. Because many of the complications arise due to the overwhelming systemic immune response in meningitis, most experts recommend early administration of steroids in addition to antibiotics.

In 2002, an important paper demonstrated the overall benefit of early administration of intravenous dexamethasone in European adults with community-acquired bacterial meningitis.[1] In that study, the risk of unfavorable outcomes was reduced from 25% to 15% in the patients randomized to dexamethasone as compared to placebo. More specifically, at 8 weeks after randomization, 11 of 157 (7%) patients died in the dexamethasone group and 21 of 144 (15%) patients died in the placebo group ($P = 0.04$).

In the current study, the authors presented the long-term mortality data on this original cohort of patients to determine whether this mortality benefit was durable. This analysis was especially important in light of another recent study[2] demonstrating that in meningitis due to tuberculosis, the benefit of steroids was only an early effect, and patients who received steroids actually "caught up" to the placebo group in terms of mortality over time.

The authors used the national database of the Netherlands to track mortality of the original cohort of patients. Of these patients, 93% could be followed. By 2011 (median follow-up of 13 years after enrollment), 31 of 144 (22%) patients in the dexamethasone group had died and 44 of 134 (33%) patients in the placebo group had died. Over the follow-up period after the primary outcome measure at 8 weeks, 20 additional patients in the dexamethasone group and 23 additional patients in the placebo group had died. After the initial 8 weeks of enrollment, the slope of the survival curves did not change between the groups. The beneficial effect in long-term survival was most apparent in the group of patients with pneumococcal meningitis.

■ COMMENTARY

This study demonstrated that the initial benefit of steroids on mortality of patients with bacterial meningitis continues to be apparent over the subsequent years. There is no additional benefit to steroids after the 8-week period, but the steroid group maintains a durable, long-term survival advantage over the placebo group. This is the first study to demonstrate this degree of long-term mortality benefit and should serve to reassure physicians that there is no long-term delayed detrimental effect on mortality when treating bacterial meningitis patients in the acute setting with dexamethasone. In fact, the early benefit endures for many years to come. ■

References

1. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002;347:1549-1556.
2. Torok ME, et al. Dexamethasone and long-term outcome of tuberculosis meningitis in Vietnamese adults and adolescents. *PLoS One* 2011;6:e27821. doi: 10.1371/journal.pone.0027821.

The Coronaries Were Clean...

ECG REVIEW

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

This article originally appeared in the December 15, 2012, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Brunton serves on the advisory board for Abbott, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Kowa, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

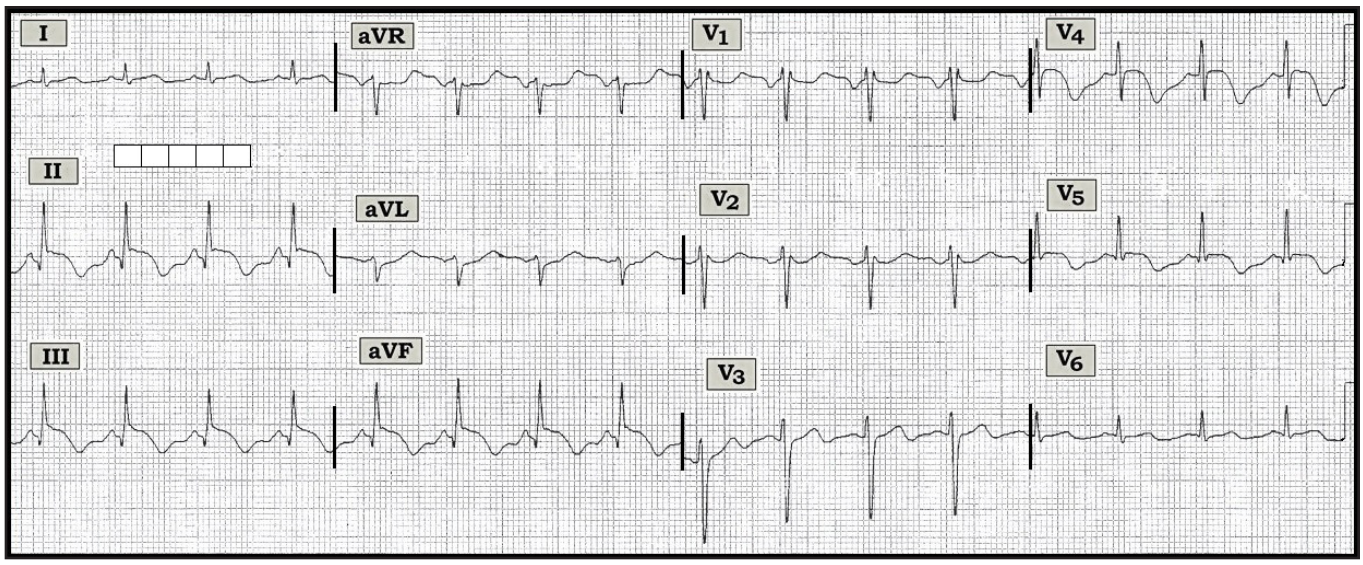

Figure — ECG obtained from a 74-year-old woman with renal colic but no chest pain.

Scenario: The ECG shown above was obtained from a 74-year-old woman who presented with abrupt onset of severe renal colic but no chest pain. Based on findings seen in her ECG, acute cardiac catheterization was performed. Her coronary arteries were normal on cath. Troponins were only minimally elevated. How would you interpret her ECG? How might you explain the finding of normal coronary arteries on cardiac catheterization?

Interpretation: The ECG shows sinus rhythm at a rate close to 100/minute. The PR and QRS intervals appear to be normal, but the QT is prolonged. The axis is normal (approximately +70 degrees). There is no chamber enlargement. An rSr' complex is noted in lead V1.

Assessment of QRST changes is remarkable for the presence of inferior Q waves — normal transition (R wave becoming taller than the S wave between leads V3-to-V4) — and ST segment coving with marked elevation in the inferior leads. This is accompanied by deep T wave inversion. Similar abnormal ST segment coving and elevation (albeit not as marked) is also present in leads V4 and V5. Deep, symmetric T wave inversion that begins in lead V3 is seen in V4 and V5.

Despite the absence of chest pain, the impression from interpretation of this ECG was "probable acute ST-elevation myocardial infarction in need of immediate cardiac catheterization for possible reperfusion." Surprisingly, cardiac catheterization revealed normal coronary arteries. Instead, the ventriculogram revealed apical ballooning with hypercontractility of the cardiac base characteristic of Takotsubo cardiomyopathy. The patient was treated supportively with recovery of left ventricular function over the next few weeks.

Takotsubo cardiomyopathy is an underappreciated cause of acute ECG abnormalities and new-onset heart failure. The entity was first described in Japan in 1990, with the name takotsubo being derived from a specially designed container used by Japanese fishermen to trap octopuses. The unusual round bottom and narrow neck design of takotsubo resembles the diagnostic picture on cardiac catheterization obtained as a result of ballooning of the cardiac apex with hypercontraction of the base. Other names attributed to this syndrome include stress cardiomyopathy and broken-heart syndrome, in reference to the common occurrence of severe physical or emotional stress prior to onset of the disorder. Awareness of this syndrome is important because the initial ECG may mimic a large apical infarction (with inferior and anterior ST segment elevation). Transient heart failure is common during the initial stages, but fortunately resolves within a few weeks in most cases.

For more information on this ECG Review and Takotsubo cardiomyopathy, please visit: https://www.kg-ekgpress.com/ecg_-_takotsubo/. ■

CME / Objectives

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

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems. ■

CME Questions

1. In the study on long-term outcomes after bacterial meningitis, Fritz and colleagues demonstrated that, compared to placebo, the use of dexamethasone:

a. Increased the risk of death at both 8 weeks and 5 years.

b. Decreased both the short-term and the long-term risk of death.

c. Decreased the risk of death but increased the incidence of Diabetes mellitus.

d. Decreased the short-term risk of death but this effect was lost by 1 year.

2. In the meta-analysis for central venous catheters and catheter-related bloodstream infection (CRBSI), Marik, et al., demonstrated that:

a. The use of the subclavian vein was superior to the internal jugular vein that was in turn superior to the femoral vein with regards to CRBSI.

b. The risk for deep-venous thrombosis (DVT) was increased with the femoral vein site.

c. There was no significant difference in risk for CRBSI between the femoral and subclavian sites.

d. There has been no change in CRBSI rates over time despite the use of the central line bundle.

3. Which of the following observations were made in the two studies about rapid response teams:

a. Housestaff and nurses favored the use of the rapid response team to help them realign their workload.

b. Nurses value the ability to summon a highly experienced team to the bedside of an unstable patient.

c. Patients with a rapid response team activation were more like to be transferred to the ICU if they met threshold vital sign abnormalities.

d. All of the above.

CME Instructions

1. Read and study the activity, using the provided references for further research.

2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the evaluation is received, a credit letter will be sent to you. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

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 2 PAGES 3-4 FEBRUARY 2013

Does Screening for Type 2 Diabetes Pay Off?

Source: Simmons RK, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): A cluster-randomised controlled trial. *Lancet* 2012;380:1741-1748.

IT IS EASY TO ENVISION THAT EARLIER DIAGnosis of type 2 diabetes (DM2) might lead to an opportunity for earlier, intensified interventions that might translate into improved outcomes. So far, however, we only *think* that, we don't actually *know* it. Simmons et al followed patients from general practices in England (n = 11,737) who enrolled in pathways of 1) screening for DM2 plus intensive multifactorial interventions, 2) screening for DM2 plus routine care, and 3) a "no screening" population. The mean age of the population was 58 years.

The practices in which multifactorial intervention groups were enrolled received educational and logistical support for attaining glucose, blood pressure, and lipid goals. Recent data in the United States suggest that currently fewer than 15% of type 2 diabetics are achieving simultaneous goal attainment in all three of these.

Over an interval of approximately 10 years' follow-up, there were no significant differences seen between unscreened vs screened subjects in regards to all-cause mortality, cardiovascular mortality, cancer mortality, or diabetes-related death.

Explanations for failure to reduce risk include the following: 1) screening for diabetes became more routine in the non-screened group over time; 2) routine care is improving, such that intensive intervention may not be as dramatically different than routine care, and 3) the duration of follow-up was insufficient. ■

Surgical Treatment of Diabetes

Source: Vetter ML, et al. Comparison of bariatric surgical procedures for diabetes remission: Efficacy and mechanisms. *Diabetes Spectrum* 2012;25:200-210.

THE LINK BETWEEN OBESITY AND TYPE 2 diabetes (DM2) is widely acknowledged. Certainly, weight gain is associated with increased incidence of DM2, and weight loss improves insulin sensitivity, as well as other cardiovascular risk factors. Surgery produces prompt and dramatic reductions in excess body weight, yet it appears that rebalancing of the disturbed metabolic homeostasis seen in DM2 varies among the different bariatric surgical interventions. Additionally, it appears that weight loss alone cannot fully explain the metabolic restorations seen post-surgically. Favorable metabolic changes are especially prompt, intensive, and durable when surgery involves bypassing or elimination of much of the small intestine from the digestive path.

In their review of the DM2 bariatric surgery trials, Vetter et al conclude that the primary driving force for DM2 remission appears to be weight loss. Since diversionary procedures are associated with greater and more durable weight loss, they would be anticipated to produce greater benefits for DM2 and they do. Overall adjustable gastric bypass is reported to result in remission in 57% vs 95% in biliopancreatic diversion surgery. The long-term relapse rate is not insubstantial: One very long follow-up of diversionary surgery (up to 16 years) noted relapse in 43%.

There are distinct hormonal changes that differ between the surgical interventions. For instance, gastric banding does not affect incretin activity, but bypass surgeries are associated with increased secretion of incretins. Evidence continues to accumulate that corroborates the efficacy, safety, and durability of bariatric surgical intervention for DM2. ■

Benefits and Consequences of Aldosterone Antagonists for HF

Source: Hernandez AF, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. *JAMA* 2012;308: 2097-2107.

CLINICAL TRIAL DATA HAVE CONCLUSIVELY demonstrated improved mortality and cardiovascular outcomes in chronic heart failure (CHF) patients who receive aldosterone blockade (ALD) with spironolactone or eplerenone in addition to standard of care treatment. Clinical trial populations, however, are different from practice settings in which patients may not enjoy the same risk:benefit balance as the often highly selected subjects who enroll in clinical trials.

To evaluate outcomes among patients

with newly administered ALD *not* enrolled in a clinical trial, Hernandez et al reviewed 2005-2010 Medicare data on older (mean age, 78 years) patients who had received a new ALD prescription on discharge from the hospital for CHF (n = 5887). They looked at all-cause mortality, cardiovascular readmission, heart failure readmission, and hyperkalemia.

Although there was no difference in total mortality, the addition of ALD to the treatment regimen was associated with lower heart failure readmission. On the other hand, patients treated with ALD were statistically significantly more likely to be readmitted with hyperkalemia over the next year (1.5-2.5 times more likely). ALD treatment offers some positive outcomes, but clinicians must be vigilant for hyperkalemia when ALD treatment is chosen. ■

Long-term Prevention of Recurrent DVT

Source: Brighton TA, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012; 367:1979-1987.

Current guidelines for management of venous thrombosis (e.g., the Antithrombotic 9 guideline published by the American College of Chest Physicians in 2012) suggest that after an initial episode of unprovoked deep venous thrombosis (DVT), it is reasonable to provide at least a 3-month course of anticoagulation, with consideration of a longer interval on a case-by-case basis. Usually, anticoagulation is not continued long-term. But the risk of DVT recurrence after cessation of coumadin is not insignificant.

Aspirin (ASA) is easy to administer and has a generally favorable risk profile. After cessation of coumadin, Brighton et al compared DVT patients treated with aspirin vs placebo for approximately 3 years. Although numerically fewer recurrent DVT episodes occurred in the ASA group, the numbers did not achieve statistical significance (4.8%/yr vs 6.5%/yr; P = 0.09). On the other hand, ASA produced a reduction in secondary composite outcomes, which included myocardial infarction, stroke, and cardiovascular death. Hence, even though ASA did not produce a statistically significant reduction in DVT, the potential reduction in other cardiovascular adversities might tip the balance toward benefit. Because the primary endpoint of the trial was not met, secondary endpoints, however, must be considered hypothesis generating rather than conclusive. ■

Marijuana and the Risk of Schizophrenia

Source: Evins AE. The effect of marijuana use on the risk for schizophrenia. *J Clin Psychiatry* 2012;73:1463-1468.

The recent legalization of marijuana in two states has brought the discussion of potential toxicity to the fore. Although it is unclear what impact legalization will have on epidemiology of marijuana use, most experts agree that more widespread and heavier marijuana use would not be at all surprising. The psychiatry community has particular concern about marijuana use because observational data suggest that early (during adolescence) marijuana use is associated with an increased risk for an earlier onset of schizophrenia.

Most schizophrenia is genetic in origin (80%). Hence, if marijuana is a contributor to schizophrenia, it occurs in a minority of cases. On the other hand, some genetic predilection for development of schizophrenia can be seen in carriers of the Met allele of the COMT gene, who appear especially likely to develop psychosis subsequent to cannabis use in adolescence.

At the current time, experts suggest advising parents that marijuana use in adolescence, especially heavy use, may increase the risk of future schizophrenia, and for persons with existing psychosis, may make symptoms worse. ■

Losartan Improves Erectile Function in Diabetics

Source: Chen Y, et al. Losartan improves erectile dysfunction in diabetic patients: A clinical trial. *Internat J Impot Res* 2012; 24:217-220.

Animal studies have shown that high levels of angiotensin II (ANG2) in the corpora cavernosa of the penis extinguish erections, the effect of which can be blocked by losartan, an ANG2 receptor blocker. Whether losartan might have a favorable effect on erectile dysfunction (ED) in diabetic humans has not been definitively confirmed.

Chen et al studied diabetic adults with ED (n = 124) who were randomized to receive either LOS 50 mg/d alone, tadalafil 5 mg/d (TAD) alone, the combination of LOS + TAD, or no treatment for 12 weeks. Persons with poorly controlled hypertension were excluded from the trial.

At the conclusion of the trial, TAD and LOS provided comparable significant improvements in erectile function scores, but the LOS + TAD combination was significantly better than either monotherapy. The control group experienced no significant improvement in erectile function. LOS was very well tolerated, and tolerability was not compromised by combining LOS + TAD. Clinicians might consider the addition of LOS to patients with insufficient ED response to TAD alone. ■

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

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, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

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.*

FDA Approves Apixaban for Patients with Nonvalvular AF

In this issue: Apixaban approval; new dental clinical practice guideline; apixaban for VTE; aspirin resistance; tamoxifen treatment; and FDA actions.

Apixaban superior to warfarin in trial

The FDA has approved apixaban — the long-awaited third novel oral anticoagulant (NOAC) — for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The drug follows dabigatran (Pradaxa) and rivaroxaban (Xarelto) for this indication, which has been traditionally treated with warfarin. The safety and efficacy of apixaban was demonstrated in the 18,000 patient ARISTOTLE trial, which showed that in patients with nonvalvular AF, apixaban was superior to warfarin in preventing stroke and systemic embolism, caused less bleeding, and resulted in lower mortality than warfarin. The FDA will likely allow the manufacturers of apixaban to market the drug as "superior to warfarin." Apixaban is dosed twice a day, similar to dabigatran; rivaroxaban is dosed once a day. Apixaban and rivaroxaban are factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. No head-to-head studies have been done among the three NOACs, which are expected to compete aggressively for this lucrative market that is worth billions of dollars in sales. All three lack a reversal agent, which could potentially increase the risk of serious bleeding. Apixaban is marketed as Eliquis by Bristol-Myers Squibb and Pfizer. ■

New dental prophylaxis guideline

The American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association (ADA) have jointly published a clinical practice guideline regarding dental prophylaxis in patients with orthopedic implants. The recommendations, which are based on very limited evidence, state that, "the practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures." The guideline further states that they are unable to recommend for or against topical oral antibiotics in patients with implants, but they do recommend that patients with joint implants should "maintain appropriate oral hygiene," even though there is no evidence regarding this recommendation. This guideline does little to settle the debate between orthopedic surgeons, who often recommend lifetime dental prophylaxis, and infectious disease specialists who generally recommend against dental prophylaxis after 1 year. This rather weakly worded guideline is probably not the guidance most primary care physicians were hoping for, since they are generally responsible for prescribing prophylactic antibiotics and are responsible for possible adverse effects. The full guideline is available at www.aaos.org/research/guidelines/PUDP/dental_guideline.asp. ■

Length of treatment for VTE

How long should we treat patients with venous thromboembolism (VTE)? VTE includes deep-vein thrombosis and pulmonary embolism. Current

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.

guidelines recommend 3-6 months of anticoagulation for unprovoked VTE — usually low-molecular weight heparin followed by warfarin. A new study suggests that an additional year of the factor Xa inhibitor apixaban (recently approved for stroke prevention in nonvalvular atrial fibrillation, see page 1) may be beneficial for these patients. In an industry-sponsored study, patients with VTE who had completed 6-12 months of anticoagulation therapy were randomized to an additional 12 months of apixaban (2.5 or 5 mg twice a day) or placebo. Nearly 2500 patients were included in the intention-to-treat analysis. Recurrent VTE or death from VTE occurred in 73 of 829 patients randomized to placebo (8.8%) compared to 14 of 840 patients on 2.5 mg of apixaban (1.7%) and 14 of 813 patients on 5 mg of apixaban (1.7%; $P < 0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group and 0.2% and 0.1% in the apixaban 2.5 mg and 5 mg groups, respectively. The rate of death from any cause was 1.7% in the placebo group and 0.8% and 0.5% in the apixaban 2.5 mg and 5 mg groups, respectively. The authors conclude that extended anticoagulation with apixaban at either a treatment dose (5 mg bid) or thromboprophylactic doses (2.5 mg bid) reduced the risk of recurrent VTE without increasing the rate of major bleeding (*N Engl J Med* published online Dec. 8, 2012. doi: 10.1056/NEJMoa1207541). In this study, the majority of patients were younger than age 75 without other comorbities such as low body weight or renal impairment. It is also unknown if the results of this study are applicable to other approved anticoagulants such as rivaroxaban. ■

Aspirin resistance and enteric coating

Could "aspirin resistance" be due to enteric coating? The concept of aspirin resistance is very controversial with some experts suggesting that it does not exist. A new study suggests that enteric coating of aspirin may be partially responsible for "pseudoresistance." Researchers recruited 400 healthy volunteers who were then screened for their response to a single, oral dose of 325 mg immediate-release or enteric-coated aspirin. Variable absorption caused nearly half of those taking enteric-coated aspirin to have apparent resistance (49%), while this was not seen in any of the subjects taking immediate-release aspirin. On re-exposure, all of those with variable absorption responded to aspirin. The authors conclude that the study failed to identify a single case of true aspirin resistance, but pseudoresistance, reflecting delayed and reduced drug absorption, complicates enteric-coated but not immediate-release aspirin (*Circulation* published online Dec. 4, 2012. doi: 10.1161/CIRCULATIONAHA.112.117283). This study seems to contradict the concept that up to 40% of the population is "aspirin resistant." There is a suggestion that the concept of aspirin resistance has been touted by the manufacturers of expensive brand-name aspirin substitutes. This study may question the wisdom of the routine use of enteric-coated aspirin, especially given that enteric coating has very little benefit with regard to gastrointestinal protection. ■

Is 10 years of tamoxifen better?

Ten years of tamoxifen may be better than the standard 5 years for women with estrogen receptor (ER)-positive breast cancer, according to a new study from the United Kingdom. Researchers randomized about 6800 ER-positive women with early breast cancer who had completed 5 years of adjuvant tamoxifen to another 5 years of treatment or stopping therapy. There were 617 recurrences in the 3428 women who took tamoxifen for 10 years vs 711 in 3418 women who stopped at 5 years ($P = 0.002$). There was also a lower death rate (331 vs 397, $P = 0.01$) and reduced overall mortality (639 vs 722, $P = 0.01$) in the 10-year group. There were higher rates of endometrial cancer (relative risk [RR] 1.74, 95% confidence interval [CI], 1.30-2.34) and pulmonary embolism (RR 1.87; CI, 1.13-3.07) in the 10-year group, but no higher rate of stroke and a lower risk of ischemic heart disease (RR 0.76; CI, 0.60-0.95). The authors suggest that 10 years of tamoxifen in ER-positive patients can approximately halve breast cancer mortality during the second decade after diagnosis (*Lancet* published online Dec. 5, 2012. doi.org/10.1016S0140-6736(12) 61963-1). ■

FDA actions

The FDA has approved pasireotide diaspartate injection for the treatment of Cushing's disease in patients who are not candidates for surgery or for whom surgery has not worked. The drug is considered an orphan drug. The safety and efficacy were evaluated in a trial of 162 patients with Cushing's disease who were randomized to one of two doses of the drug. About 20% of participants had normal urine cortisol levels within 6 months. Side effects included increased blood sugar levels and liver injury. The drug is administered subcutaneously twice a day. It is marketed by Novartis as Signifor. In February 2012, the FDA approved mifepristone (Korlym) for the treatment of Cushing's syndrome. ■