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HOSPITAL MEDICINE ALERT

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Oral Vitamin K for Excessive Anticoagulation

ABSTRACT & COMMENTARY

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

This article originally appeared in the April 2009 issue of Clinical Oncology Alert. *It was edited by William B. Ershler, MD, and peer reviewed by V.R. Veerapalli, MD. Dr. Ershler is works for INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC, and Dr. Veerapalli is Staff Clinician, INOVA Fairfax Cancer Center, Falls Church, VA. Dr. Ershler is on the speaker's bureau for Wyeth, and does research for Ortho Biotech, and Dr. Veerapalli reports no financial relationships relevant to this field of study.*

Synopsis: *Whether oral vitamin K reduces the risk of bleeding related to excessive anticoagulation from warfarin remains unclear. Across 14 anticoagulation clinics, 724 patients with an asymptomatic elevated INR between 4.5 and 10.0 were randomized to 1.25 mg of oral vitamin K or placebo. Within the first 90 days, 15.8% in the vitamin K group and 16.3% in the placebo group had at least one bleeding episode (p = 0.86). There were no differences in major bleeding, thromboembolism, or death. The INR fell more quickly in the vitamin K group. Oral vitamin K does not substantially reduce the bleeding in warfarin-treated patients with an INR from 4.5 to 10.0.*

Source: Crowther M, et al. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin. *Ann Intern Med*. 2009;150:293-300.

WARFARIN IS A FREQUENTLY PRESCRIBED ORAL ANTICOAGULANT. The highly variable, dose-response characteristics mandate monitoring, and this is usually accomplished by targeting an international normalized ratio (INR) value between 2.0 to 3.0. Non-therapeutic values are common, and values above 4.5 predispose to serious bleeding.[1] Low-dose oral vitamin K can effectively reduce the INR within 24 hours in patients excessively anticoagulated from warfarin.[2] In this study, Crowther et al evaluated whether low-dose vitamin K would reduce bleeding relative to withholding warfarin alone in non-bleeding patients with a high INR from warfarin.

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Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, selected and reviewed the articles contained within this issue on April 10, 2009.

Adult patients from anticoagulation clinics were eligible if an outpatient INR was found to be 4.5-10.0 within the past 24 hours; the target INR was 2.0-3.5, with no bleeding. Patients with other risk factors for bleeding, or a need for acute normalization of the INR, were excluded. Patients were randomized to receive a formulated capsule of 1.25 mg of oral vitamin K or placebo. Patients were followed in person or over the telephone for 90 days to assess the primary endpoint of bleeding within 90 days of randomization. The INR was managed as per local practice. The mean age of enrolled patients was 69 years, and the mean INR at enrollment was 5.8 to 6.0 among the 724 enrolled patients. In the vitamin K group, 56 of 355 (15.8%) experienced a bleeding event compared to 60 of 369 (16.3%) in the placebo group. Major bleeding occurred in 2.5% and 1.1% in the vitamin K and placebo groups, respectively. There were no significant differences for the bleeding event ($p = 0.86$), major bleeding events ($p = 0.22$), thromboembolism ($p = 0.72$), or death ($p = 0.94$) by day 90. The average decrease in the INR the following day was 2.8 units for the vitamin K-treated patients but only 1.4 units for the placebo patients ($p < 0.001$).

■ COMMENTARY

Warfarin has found widespread use as an anticoagulant to prevent venous and arterial thrombosis. Despite a host of new anticoagulants, the low cost and familiarity with warfarin promote its continued use, as well as alternative management models such as telephone monitoring.[3] Supratherapeutic INR values are not uncommon, predispose to bleeding, and represent a management challenge. Multiple studies have shown that for high INR values, low doses of oral vitamin K can hasten correction, compared to holding warfarin alone.[2] It is unknown whether an asymptomatic patient with an incidentally elevated INR benefits from low-dose vitamin K.

In this study, Crowther et al randomized patients with an asymptomatic, newly elevated INR from 4.5 to 10.0 to receive 1.25 mg of oral vitamin K or placebo. They found no difference in any of the study endpoints of bleeding at 30, 60 or 90 days. The primary outcome of bleeding at 90 days was around 16% in both groups. No differences were found in major bleeding, new thromboembolism, or death. The data support a strategy of withholding warfarin without giving oral vitamin K for asymptomatic elevations of the INR.

Interestingly, only three serious bleeding events occurred among all subjects in the first seven days, two from placebo-treated patients and one case in a vitamin K-treated patient. Thus, these data suggest outpatient management appears safe, at least for those meeting the protocol criteria.

As noted by Crowther et al, the study was not powered to detect small differences in bleeding between each arm. The largest limitation rests with the restrictive criteria of a randomized study that limits generalizability. These patients were being followed closely at an anticoagulation clinic. In addition, patients at higher risk of bleeding were not included, such as those who already had bleeding, INR levels above 10.0, low platelets, or liver disease. Although data are lacking, it may be reasonable for such higher-risk patients to receive oral vitamin K. The data in this study were at least reassuring that thromboembolism was no more frequent in the vitamin K-treated patients. For patients having overt or serious bleeding, more immediate corrective actions will be needed. A practical problem related to the 1.25 mg dose of vitamin K is not readily available. However, the 2.5 mg dose could be broken in half, or an alternative is to use a 1 mg tablet.

In conclusion, low-dose oral vitamin K correction does not reduce bleeding risk for asymptomatic supratherapeutic elevations of the INR from warfarin. ■

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Questions & Comments

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MRSA Central-Line Bacteremias Decline in U.S. ICUs

ABSTRACT & COMMENTARY

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This article originally appeared in the April 2009 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Price is Assistant Professor, University of Colorado School of Medicine. Dr. Deresinski is on the speaker's bureau for Merck, Pfizer, Wyeth, Ortho-McNeill (J&J), Schering-Plough, and Cubist, does research for the National Institute of Health, and is an advisory board member for Schering-Plough, Ortho-McNeill (J&J), and Cepheid. Dr. Price reports no financial relationships relevant to this field of study.*

Synopsis: *Surveillance data from the CDC show that central-line associated bloodstream infections due to methicillin-resistant* Staphylococcus aureus *in U.S. intensive care units showed an overall decrease of 50% during 1997-2007. There was a concomitant decline in infections due to methicillin-susceptible* S. aureus *total central-line-associated BSIs during that period as well. The reason for this favorable change in infection rates is not ascertainable from the surveillance data.*

Source: Burton DC et al. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997-2007. *JAMA*. 2009;301:727-736.

Data collected from the CDC's two surveillance systems[1] for hospital-acquired infections tracked the rate of central-line-associated blood stream infections (CLA-BSIs) from 1997-2007. Data were not collected in 2005 during the transition between the two systems. A total of 1,684 ICUs reported CLA-BSI data to the CDC. The reporting facilities changed during the period, as facilities entered or left the program. Prior to 2007, the median number of facilities participating was 244; in 2007 the number increased to 518. The rate of MRSA CLA-BSI increased significantly from 1997 to 2001, from 0.3 to 0.4 cases per 1,000 central line days, then fell significantly from 2001 to 2007, reaching 0.2 cases per 1,000 central line days. The overall decline during the entire reporting period was 49.7%. During the entire 11-year reporting period, the rate of CLA-BSI due to methicillin-susceptible *S. aureus* declined steadily from 0.3 to 0.09 cases per 1,000 patient days, a 70% reduction. During the same period, there was a continuous and significant decrease in the rate of CLA-BSIs due to all pathogens; this decrease was consistent across ICU types.

■ COMMENTARY

To begin with, I have a quibble with the title. It would be more accurate to bill this as "central-line-associated bloodstream infections declined substantially. . .but the decline in MRSA infections took a bit longer." MRSA accounted for less than 10% of CLA-BSIs in the units studied, and the change in the rate of MRSA infection is a very small contributor to the overall change in the rate of CLA-BSIs.

Having said that, this report shows that CLA-BSIs are clearly decreasing in ICUs — at least among those reporting through NNIS and, later, NHSN. There are some weaknesses in the way that the data were collected. Facilities entered and left the system during the reporting period, and the number of facilities participating was substantially higher in the final year of the system than in the earlier years. This could introduce reporting bias, as facilities volunteering to participate, or to continue to participate for prolonged periods of time, may be significantly different than other facilities. They may, for example, be more invested in active infection prevention. However, Burton et al examined the trends in CLA-BSIs among facilities participating during the entire reporting period and noted a decline in infection rates due to all pathogens similar to that observed in the larger group, providing reasonable assurance that there wasn't systematic bias based on the population of reporting facilities. The overall rate of catheter usage in ICUs remained stable over that period. Further, the rate changes were consistent across medical, surgical, and combined medical-surgical units.

This is certainly good news for patient safety. However, the impressive numbers leave a very large unanswered question: What was the reason for this decline in CLA-BSIs? New CDC guidelines on prevention of CLA-BSIs were published in 2002,[2] but this is unlikely to have had a dramatic effect for several reasons. First, the rates of infection due to methicillin-susceptible *S. aureus* and to all pathogens declined continuously starting in 1997. Although the reversal in the rise of the rate of MRSA CLA-BSIs was temporally associated with the guidelines, a cause-and-effect relationship is unlikely since the guidelines target infections generally, not one antibiotic resistant organism.

During the same period of the study, healthcare- and device-associated infections due to MRSA increased in the United States,[3] suggesting that the declines in overall CLA-BSIs and MRSA CLA-BSIs were independent of any MRSA control efforts.

The NNIS and NHSN data collection methodology isn't designed to answer the question. It would have been quite useful to have been able to identify any changes in practice that were associated with the decrease in infection rates. Changes in insertion techniques, catheter care, or catheter composition (i.e., antimicrobial coatings) are all potential contributors to improvements in the rates of CLA-BSIs. Unfortunately, surveillance data alone cannot provide us with any insight in that regard. Even though the data are very encouraging, it's frustrating to know the "what" without understanding the "why." ■

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Clopidogrel Plus Proton-Pump Inhibitors

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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This article originally appeared in the April 2009 issue of Clinical Cardiology Alert. *It was edited by Ethan J. Weiss, MD. Dr. Weiss is Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco; he reports no financial relationships relevant to this field of study.*

Source: Ho PM, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301:937-944.

SINCE THE RISK OF GASTROINTESTINAL BLEEDING IS increased when clopidogrel is added to aspirin therapy in patients with acute coronary syndromes (ACS), many prescribe proton-pump inhibitors (PPIs) to reduce this risk. However, mechanistic studies suggest that PPIs may reduce the effectiveness of clopidogrel. Thus, Ho et al used a Veterans Affairs national cohort to compare rates of mortality and rehospitalization for ACS between patients taking clopidogrel alone vs. clopidogrel plus PPIs. This was a retrospective cohort study of all patients with ACS discharged from any VA hospital beginning in 2003 and ending in 2006 who were prescribed clopidogrel and who filled the prescription; pharmacy refill data was used to see if the patient was on PPIs over the course of the study. Of the 8,205 identified patients on clopidogrel, 64% were given PPIs. The latter patients were older and had more co-morbidities. During a median follow-up of 521 days, 21% were re-admitted for ACS without PPIs vs. 30% on PPIs (OR 1.25, 95% CI 1.11-1.41). Also, mortality was significantly higher in the clopidogrel plus PPI group (20% vs. 17%, $p = 0.001$). Among those prescribed a PPI, 60% were given omeprazole and 37% were prescribed more than one PPI. Use of PPIs without clopidogrel in ACS patients was not associated with increased adverse outcomes. Ho et al concluded that the use of clopidogrel plus PPIs after discharge for ACS was associated with an increased risk of adverse outcomes vs. patients on clopidogrel alone.

■ COMMENTARY

The strength of this longitudinal observational study was that drug use was assessed over the duration of follow up, not just at hospital discharge, thus strengthening the conclusion that concomitant PPI and clopidogrel use after ACS leads to increased subsequent coronary events. Sensitivity analyses in this study also showed a consistent effect across subgroups.

The most common event was re-hospitalization for ACS, which substantiates the mechanistic theory that PPIs affect clopidogrel's effectiveness as a platelet aggregation inhibitor. The presumed mechanism is that both drugs are metabolized by the liver CYP2C19 cytochrome P450 isoenzyme; mechanistic studies have demonstrated this drug interaction. Poly-morphisms of the CYP2C19 gene have also shown reduced effectiveness of clopidogrel and increased cardiovascular events. Although platelet aggregation studies were not done in this large observational study, the results certainly make sense based upon what we know about these drugs.

Until more definitive studies are done, it would seem prudent to not use PPIs prophylactically for dual antiplatelet therapy but reserve it for those with other important indications. Alternatively, one could use hydrogen-blocking drugs, which do not use the P450 system, or pantoprazole, which also does not use the P450 system. Another confounding issue is that omeprazole is now available over the counter, so patients will need to be advised about indiscriminant use of this drug. Finally, if the new thienopyridine prasugrel is approved by the FDA, it may avoid this issue because it does not use the P450 system. ■

Dronedarone: New and Improved Amiodarone?

ABSTRACT & COMMENTARY

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This article originally appeared in the April 2009 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, and peer reviewed by Ethan J. Weiss, MD.*

Source: Hohnloser SH. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360: 668-678.

DRONEDARONE IS A NEW ANTIARRHYTHMIC DRUG WITH structural similarities to amiodarone. During development of the molecule, the steps included removal of the iodine atoms and making the compound more lipophilic; the latter produces a shorter elimination half-life and reduced tissue accumulation. The primary goal was to reduce the risk for organ toxicity, especially thyroid, pulmonary, and hepatic adverse events. The ATHENA trial was a placebo-controlled study designed to determine whether dronedarone would reduce cardiovascular hospitalizations and deaths in patients with atrial fibrillation.

Initially, patients were eligible for inclusion in the trial if they had a history of paroxysmal or persistent atrial fibrillation and were either at least 70 years old or younger but had a risk factor for stroke or death. Subsequently, however, the entry criteria were modified such that patients between 70 and 75 years of age had to have at least one additional risk factor. Patients older than 75 continued to be eligible even if they had no additional risks. Patients younger than age 70 were no longer eligible. Patients were excluded from the study if they had permanent atrial fibrillation, a recent episode of decompensated heart failure or current New York Heart Association class IV symptoms, acute myocarditis, or significant bradycardia. Patients could be either in sinus rhythm at the time of enrollment or have a cardioversion planned. The primary study outcome was a composite endpoint that included a first hospitalization due to a cardiovascular event or death from any cause. Unplanned hospitalizations were classified as cardiac or non-cardiac in a blinded fashion by an events committee. Secondary study outcomes were death from any cause, death from cardiovascular cause, and first hospitalization due to a cardiovascular event.

ATHENA enrolled 4,620 patients; 2,301 in the dronedarone group and 2,327 in the placebo group. The mean age was 71.6 years, and 47% of the patients were women. Hypertension was the predominant underlying cardiovascular disease seen in 87% of the patients. Although 21% of the patients had a history of New York Heart Association class II or III heart failure, only 11.9% and 3.9% of the patients had a left-ventricular ejection fraction below 45% or 35%, respectively.

The median duration of follow-up was 22 months. Dronedarone was superior to placebo in terms of the primary outcome event. Among patients who received dronedarone, 675 patients (29.3%) had their first cardiovascular hospitalization and 59 (2.6%) patients died without prior hospitalization. In the placebo group, there were 859 (36.9%) first cardiovascular hospitalizations and 58 deaths before hospitalization (2.5%). The hazard ratio (HR) for the composite primary outcome was 0.76 (95% confidence interval [CI] 0.69 to 0.84; $p < 0.001$). Subgroup analysis showed a consistent beneficial effect of dronedarone across several important subgroups. Analysis of the secondary endpoints also favored dronedarone. There

was a trend toward reduced total mortality in the dronedarone group, with 116 (5%) deaths in that group compared to 139 (6.0%) in the placebo group (HR 0.84, $p = 0.18$). Cardiovascular deaths were significantly reduced.

In the dronedarone group, there were 63 cardiovascular deaths (2.7%), compared to 90 cardiovascular deaths in the placebo group (HR 0.71, 95% CI, 0.51 to 0.98; $p = 0.03$). There were no significant differences between the groups in deaths resulting from cardiac arrhythmia. Atrial fibrillation recurrence was not an endpoint, but the reduction in cardiovascular hospitalization was driven mainly by a reduction in the number of hospitalizations for atrial fibrillation. There were 510 hospitalizations for atrial fibrillation in the placebo group vs. 335 (14.6%) in the dronedarone group. (HR 0.63, $p < 0.001$). There were no significant differences between the groups in number of hospitalizations for heart failure, syncope, or ventricular arrhythmias. There was a small decrease in the number of hospitalizations for acute coronary syndrome, with 62 (2.7%) in the dronedarone group and 89 (3.8%) in the placebo group (HR = 0.70; $p = 0.03$). Premature discontinuation of the study drug was observed in 30.2% of the patient receiving dronedarone compared to 30.8% of those receiving placebo. Presumed adverse events leading to discontinuation were seen in 12.7% of the patients in the dronedarone group vs. 8.1% in the placebo group. The most common significant adverse events observed with increased frequency in the dronedarone group were bradycardia, QT interval prolongation, gastrointestinal events, rash, and serum creatinine increase. There was no difference in the frequency of respiratory events, abnormal liver function tests, or thyroid dysfunction between the two groups. One case of polymorphic ventricular tachycardia with a long QT interval was observed in a 66-year-old woman on dronedarone during recovery from a previous out-of-hospital cardiac arrest. No other cases of torsades de pointes were documented.

Hohnloser et al concluded that dronedarone is associated with a significant reduction in the rate of hospitalization due to cardiovascular events or death, with a favorable side effect profile.

■ COMMENTARY

The criteria used to evaluate the efficacy of antiarrhythmic drugs in patients with atrial fibrillation need to be specific for the patient population studied. Among patients with frequent and highly symptomatic paroxysmal atrial fibrillation, changes in symptoms scores, the frequency and duration of episodes, and the need for hospitalizations are the primary useful measures. Among older patients with less frequent or less symptomatic episodes of atrial fibrillation, cardiovascular hospitalization, stroke, and death are more meaningful outcomes to measure. The ATHENA trial was the first really large study to use these new standards. In contrast to most prior antiarrhythmic drug studies, which have typically involved only several hundred patients, ATHENA included more than 4,600 subjects. The study did not really attempt to document recurrent atrial fibrillation, but rather focused on hospitalizations, many, but not all, of which were due to recurrent arrhythmia and death. Since dronedarone has effects to both prevent recurrent atrial fibrillation and also improve heart rate control during recurrent atrial fibrillation, this trial design highlights the benefits of a drug with more than one potentially beneficial activity.

It's important to note that patients with severe systolic heart failure were not included in ATHENA. Only a small number of patients had depressed left ventricular ejection fractions, and patients with recent or current decompensated heart failure were excluded. Another study of dronedarone, the ANDROMEDA trial, enrolled patients soon after a hospitalization for decompensated heart failure. In ADROMEDA, dronedarone was associated with increased mortality in the early phases, and the study was stopped by its Data Safety Monitoring Board. It has been hypothesized that some of this effect may have been due to reductions or discontinuation of ACE inhibitors or angiotensin receptor blockers in response to an early rise in serum creatinine after dronedarone was started. Investigators in ATHENA were aware that dronedarone can increase serum creatinine values without affecting the glomerular filtration rate and were instructed not to change therapy for minor creatinine elevations. However, the safety of dronedarone in patients with advanced heart failure with left-ventricular systolic dysfunction remains uncertain, and further data are needed before dronedarone can be recommended for use in such patients. ■

Greater In-hospital Use of Clinical IT is Associated with Better Patient Outcomes

By David J. Pierson, MD

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

This article originally appeared in the April 2009 issue of Critical Care Alert. *It was edited by William Thompson, MD. Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington; he reports no financial relationships relevant to this field of study.*

Synopsis: *In this study of physician use of clinical information technology in relation to 4 common diagnoses in 41 urban hospitals in Texas, inpatient outcomes were better the more extensive the use of computerized order entry, test results, physician charting, and decision support. Increased use of IT was also associated with significantly lower costs for all hospital admissions.*

Source: Amarasingham R, et al. Clinical information technologies and inpatient outcomes: A multiple hospital study. *Arch Intern Med* 2009;169:108-114.

To determine whether relationships existed between the use of clinical information technology (CIT) and measures of patient outcomes, Amarasingham et al conducted a cross-sectional study of urban hospitals in Texas using the questionnaire-based Clinical Information Technology Assessment Tool, which measures a hospital's level of automation based on the interactions of its physicians with the information system. They sent surveys to 7,432 randomly selected physicians practicing at 72 hospitals in 10 targeted urban areas in Texas, and included in the data analysis only hospitals from which five or more attending physicians returned the questionnaire. They then merged the results with data from a comprehensive hospital claims data file on 167,233 patients older than age 50 who were admitted to those hospitals with any of four diagnoses: myocardial infarction, congestive heart failure, coronary artery bypass grafting, and pneumonia. Dependent variables studied in relation to CIT use were inpatient mortality, complications, costs, and length of stay. The aspects of hospital CIT examined were computerized order entry, test results, automation of notes and records, and decision support.

Sufficient responses for inclusion were received from 41 (58%) of the hospitals. Considering the four targeted medical conditions together, a 10-point increase in the automation of notes and records was associated with a 15% decrease in hospital mortality (adjusted odds ratio [AOR], 0.85; 95% confidence interval [CI], 0.74-0.97). Hospitals with higher scores on computerized order entry had 55% decreases in hospital mortality for coronary artery bypass grafting, and 9% decreases for myocardial infarction. Higher usage of computerized decision support was associated with a 16% decrease in complications (AOR, 0.84; 95% CI, 0.79-0.90) for all four diagnoses. In addition, higher scores on computerization of test results, order entry, and decision support were associated with lower costs per hospital admission (reductions of $110, $132, and $538, respectively; $p < 0.05$). Thus, hospitals with automated notes and records, order entry, and clinical decision support had fewer complications, decreased inpatient mortality, and lower costs.

■ COMMENTARY

While perhaps not surprising, the results of this study provide solid support for the concept that CIT in hospitals is a positive development. An important strength of this study is that the findings were derived not just on the basis of which hospitals had more extensively developed CIT systems, but from data on actual use of these systems by the physicians caring for patients in those hospitals — or, at least, on how those physicians indicated on a questionnaire that they used them.

Of course, the fact that outcomes were better in hospitals with more extensive use of CIT does not establish causality. In fact, it is very likely that, overall, hospitals with more highly-developed CIT systems are also better at many other things, such as staff recruitment and training, physician continuing education, interdisciplinary interaction, infection control, and provision of up-to-date diagnostic and therapeutic technology. Nonetheless, it is also likely that increasing integration of CIT into daily practice is an important contributor to higher standards of care.

This was not an ICU study, although all four of the included medical conditions involve care in the ICU for the majority of patients. One would expect that the advantages accruing from the use of CIT would be amplified in the ICU, where the numbers of assessments and intervention are greater, the quantity of data generated is far greater,[1] and the pace is faster in nearly all respects than that on the regular floors. ■

Reference

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CME Questions

7. **In the study by Crowther et al., treatment with 1.25 mg of oral vitamin K, compared to placebo, in patients with excessive anticoagulation led to which of the following outcomes:**
   a. a significant reduction in major bleeding episodes related to the excessive anticoagulation.
   b. more rapid correction of the excessively prolonged INR.
   c. an increase in thromboembolic complications.
   d. a decrease in the number of deaths.

8. **Based on the clinical trial by Ho and colleagues, the use of proton pump inhibitors in patients on clopidogrel after an acute coronary syndrome led to:**
   a. a decrease in gastrointestinal bleeding.
   b. a decrease in the risk of death.
   c. a decrease in the rate of recurrent acute coronary events.
   d. an increase in the risk of adverse events including recurrent acute coronary events and death.

9. **According to the report by Hohnloser et al., a placebo-controlled trial of dronedarone in patients with atrial fibrillation led to which of the following outcomes:**
   a. a reduction in the risk of cardiovascular events or death.
   b. an increase in the risk of pulmonary fibrosis.
   c. an increase in the risk of diarrhea.
   d. All of the above

Answers: 7. (b); 8. (d); 9. (a)

CME Objectives

The objectives of *Hospital Medicine Alert* are to:

• review pertinent safety, infection control, and quality improvement practices;

• discuss diagnosis and treatment of acute illness in the hospital setting; and

• review current data on diagnostic and therapeutic modalities for common inpatient problems. ■