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ABSTRACT & COMMENTARY

Revised Anticoagulation Therapy Guidelines for Atrial Fibrillation Patients

By Tim Drake, PharmD, MBA, BCPS

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

SYNOPSIS: More patients with atrial fibrillation may receive anticoagulation, according to new recommendations.

SOURCE: Lip GYH, et al. Antithrombotic therapy for atrial fibrillation: Chest guideline and expert panel report. *Chest* 2018; Aug 21. pii: S0012-3692(18)32244-X. doi: 10.1016/j.chest.2018.07.040. [Epub ahead of print].

The decision to use antithrombotic (aspirin, clopidogrel) or anticoagulation (warfarin, apixaban, rivaroxaban) therapy to prevent stroke in patients with atrial fibrillation must account for the patients' risk for stroke compared to their risk for bleeding. The $CHADS_2$ and, more recently, the CHA_2DS_2VASc scores are used to quantify the stroke risk in patients with atrial fibrillation and provide clarification on the risk-benefit ratio of bleeding vs. stroke prevention.[2] Under previous direction, the recommendation was to consider no therapy for those with a CHA_2DS_2VASc score of 0, to offer antithrombotic therapy (aspirin) or anticoagulation therapy to patients at low stroke risk ($CHA_2DS_2VASc = 1$), and to offer anticoagulation to those patients at higher risk ($CHA_2DS_2VASc \geq 2$). Patients with a score of 2 had an annual adjusted stroke rate of 2.2%.[3]

The American College of Chest Physicians recently published new evidence-based guidelines on the use of antithrombotic therapy.[1] A list of key updates is presented below:

- While the CHA_2DS_2VASc score remains in use, the new guidelines do not consider gender in determining risk for the basis of treatment;
- Larger emphasis placed on determining low-risk patients using CHA_2DS_2VASc;
- For a non-sex risk score of 0, no antithrombotic or anticoagulation therapy is indicated;
- For a non-sex risk score of ≥ 1, consider anticoagulation therapy;
- For nonvalvular atrial fibrillation in patients without chronic kidney disease, novel oral anticoagulants (NOACs; apixaban, dabigatran, rivaroxaban) are preferred over warfarin to prevent stroke;

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- Special attention should be given to reduce modifiable bleeding risk factors;
- Dual or triple therapy with anticoagulation and antiplatelet agents should be limited, used only for a limited time after percutaneous coronary intervention and based on the patient's risk of bleeding;
- Patients with nonvalvular atrial fibrillation taking warfarin with a CHA_2DS_2VASc score of ≤ 1 do not require bridging prior surgery.

The CHA_2DS_2VASc score has been shown to accurately determine which patients are at low risk for stroke. Additionally, since the female sex criterion is only relevant as a risk factor for patients > age 65 years or with an additional risk factor, it makes sense to not use this score to determine if a patient is at low risk. Therefore, the term non-sex risk factor is used. For patients with no non-sex risk factors, the risk of stroke is very low and there is a strong recommendation not to offer therapy to reduce stroke risk.[1] NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are preferred over vitamin K antagonists (VKAs; warfarin) in patients with nonvalvular atrial fibrillation. In trials comparing NOACs vs. warfarin, NOACs have shown to be at least as safe and effective as warfarin. NOACs provide predictable anticoagulant effects, are shorter-acting, onset rapidly, and carry fewer drug/dietary restrictions compared to warfarin.[1] Data on aspirin and other antithrombotic medications have been inconsistent in showing benefit for stroke prevention. The authors of the AVERROES trial found a significant benefit with apixaban compared to aspirin with similar rates of major bleeding.[4] Thus, with the strong recommendation to use NOACs over VKAs, the safety and efficacy of the NOAC apixaban over aspirin, and the conflicting evidence of aspirin, it is reasonable to drop antiplatelet/antithrombotics from consideration to prevent stroke in patients with atrial fibrillation.[1] At every visit, providers should address bleeding risk, paying particular attention to modifiable risk factors. The HAS-BLED Score is a tool that can be used to determine bleeding risk factors, but should not be used to recommend against anticoagulation therapy. The major modifiable risk factors are blood pressure control, appropriate anticoagulation therapy/control, decreased use of nonsteroidal anti-inflammatory drugs and antiplatelet agents, moderation of alcohol intake, limited use of bridging, ending participation in high-risk activities that can cause trauma, and treatment of anemia or a low platelet count.[1]

■ COMMENTARY

The new guidelines include anticoagulation for stroke prophylaxis for patients with a CHA_2DS_2VASc score ≥ 1. A score of 1 corresponds to an adjusted stroke rate of 1.3% per year.[3] In the ARISTOTLE trial, the rate of major bleeds with apixaban was 2.13% per year.[5] Although many major bleeds can be managed and may not be as debilitating as a stroke, the risk-benefit ratio is not as clear at this level. Additionally, if warfarin is used, the risk of a major bleed increases to 3.09% per year.[5] The risk-benefit ratio is clearer when looking at only the rate of intracranial hemorrhage (0.33% per year with apixaban).[5] Finally, these factors re-enforce the importance of reducing the modifiable bleeding risk factors in patients on anticoagulation. The approximate percentage of patients with atrial fibrillation who score 1 on the CHA_2DS_2VASc scale is 9.5%.[2] With an estimated 2.7-6.1 million people in the United States with atrial fibrillation, these new recommendations could increase the number of people receiving anticoagulation by 250,000-580,000.[3] Considering that the average cost of NOACs is $500 per month, the potential increase in yearly drug cost to the U.S. healthcare system could be $1.5-3.5 billion. The decreased risk of stroke with the accompanying morbidity and mortality would need to be considered to provide a full cost-benefit analysis. ■

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ABSTRACT & COMMENTARY

Are In-hospital Deaths Related to Community-acquired Pneumonia Preventable?

By Betty Tran, MD, MSc

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

SYNOPSIS: This secondary analysis of data from five tertiary care centers found that among patients hospitalized for community-acquired pneumonia, very few deaths potentially were related to a lapse in in-hospital quality of pneumonia care.

SOURCE: Waterer GW, et al. In-hospital deaths among adults with community-acquired pneumonia. *Chest* 2018; May 30. pii: S0012-3692(18)30801-8. doi: 10.1016/j.chest.2018.05.021. [Epub ahead of print].

Although hospitalization for and subsequent mortality related to community-acquired pneumonia (CAP) is common, it is unclear whether improvements in inpatient pneumonia-related care can affect pneumonia-related mortality. A prior study showed that only about half of all deaths in patients with CAP were attributable to their acute illness.[1]

Waterer et el conducted a secondary analysis of the Etiology of Pneumonia in the Community (EPIC) study of adults hospitalized for CAP at five tertiary care hospitals (three in Chicago, two in Nashville). Notably, patients with recent prior hospitalizations, tracheotomies/gastric tubes, cystic fibrosis, neutropenic cancer, transplant, and HIV with CD4 counts < 200/mm^3 were excluded. Treating physicians made management decisions for each patient. For patients who died during their index CAP hospitalization, a five-physician panel at each study city (with expertise in emergency medicine, infectious diseases, pulmonary, and critical care) made several determinations. These included: cause of death based on *a priori* criteria; whether the cause of death was directly, indirectly (major or minor contribution), or not related to CAP; whether management was consistent with current recommendations in care quality metrics (antibiotics administered per Infectious Diseases Society of America and American Thoracic Society guidelines, antibiotics delivered within six hours of presentation or one hour [if shock present], using arterial blood gas or pulse oximetry to assess oxygenation); and whether end-of-life limitations in care existed. All five panelists discussed the cases, with complete medical records available for review until the physicians reached a consensus (four out of five or five out of five in agreement).

The authors included 2,320 adults hospitalized for CAP in the final study population. Fifty-two patients died during their CAP hospitalization. The most common causes of death were hypoxemic respiratory failure (25.0%) and septic shock (23.1%). Compared with patients who survived hospitalization, those who died were older and exhibited more comorbidities. The physician panel attributed 27 deaths directly to CAP. Panelists attributed 10 deaths to situations in which CAP played an indirect role with major contribution. Further, physicians found that nine deaths occurred when CAP played a minor role. Finally, the physicians ruled that CAP was unrelated to the other six deaths. There were DNR orders for a significant number of patients who died (21 of 52 patients). Ten had DNR orders in place prior to admission, eight after admission but > 48 hours prior to death, and three within 48 hours of death. Sixty-seven percent of in-hospital deaths occurred within the first 10 days of admission.

Among the 52 patients who died in the hospital, the physician panel identified nine who had a lapse in quality of in-hospital CAP care. However, the physicians judged five of these nine deaths to be unrelated to the lapse in care quality. Further, the physicians judged two of the nine deaths were patients who had end-of-life care limitations in which decisions were made not to pursue ICU care at the time of admission. Therefore, only two patients who were not DNR were identified to have a lapse in quality in-hospital pneumonia care, potentially contributing to in-hospital death. In one patient, there was difficulty finding intravenous access, with a subsequent delay in antibiotics. For the other patient, medical staff thought there was an intra-abdominal infection, based on an admit chest X-ray that did not show signs of pneumonia, and administered ciprofloxacin only; however, a CT scan the next day was consistent with pneumonia.

■ COMMENTARY

The authors of this prospective, multicenter study of more than 2,000 adults hospitalized for CAP found a low in-hospital mortality rate of 2.2% (52 patients) and identified only two patients for whom a lapse in in-hospital pneumonia care potentially contributed to death. As such, the authors concluded that most in-hospital deaths

among adults with CAP would not have been preventable with improved quality of in-hospital care. The study has several strengths, including review of patient cases by many physicians with clinical expertise. These physicians paid careful attention to whether CAP could be an indirect contributor (minor or major) to death based on a broad view of how acute pneumonia could lead to extrapulmonary complications (e.g., new cardiovascular disease, stroke, renal failure, secondary infection after initial stabilization of CAP). Also, the authors captured end-of-life limitations on care, which affects whether patients die in the hospital.

The most important limitation to this study is its generalizability. The five hospitals were academic, urban, U.S. facilities that maintain extensive training programs and employ clinician scientists who are dedicated to studying CAP and providing high-quality care. The relatively low mortality rate and high compliance with quality pneumonia care are reflective of this. Thus, the study's findings likely are not generalizable to other institutions, where in-hospital deaths due to CAP may be reduced by following recommended guidelines for CAP and sepsis management. This study and its case report template (available in Appendix 1 in the online supplement) would be a helpful starting point for individual hospitals to evaluate their own outcomes and guide quality improvement initiatives related to CAP hospitalizations. ■

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ABSTRACT & COMMENTARY

Home-based Detection of Undiagnosed Atrial Fibrillation

By Joshua D. Moss, MD

Associate Professor of Clinical Medicine, Cardiac Electrophysiology, Division of Cardiology, University of California, San Francisco

Dr. Moss reports he is a consultant for Biosense Webster and Abbott.

SYNOPSIS: In patients with risk factors for atrial fibrillation, screening with a self-applied wearable ECG patch resulted in significantly increased rates of new atrial fibrillation diagnoses within four months, along with greater use of anticoagulants and healthcare resources.

SOURCE: Steinhubl SR, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: The mSToPS randomized clinical trial. *JAMA* 2018;320:146-155.

Current screening for atrial fibrillation (AF) in high-risk populations generally is limited to auscultation, pulse palpation, and "spot" 12-lead ECGs during routine visits. Steinhubl et al sought to study the effect of a more aggressive but practical method of screening, using a self-applied, two-week, continuous ECG monitoring patch at home during routine activities.

The study population consisted of participants in a single large national health insurance plan, with eligible patients chosen from more than 1 million candidates based on risk factors for AF: age ≥ 75 years of age, or men > 55 years of age or women > 65 years of age with one or more comorbidities (including prior stroke, heart failure, or the combination of diabetes and hypertension, among others). Patients with any current or prior diagnosis of atrial arrhythmia who already were on anticoagulation therapy or who had an implantable pacemaker or defibrillator were excluded. More than 100,000 eligible patients were contacted, with most eventual enrollees contacted by email. Individuals who chose to enroll were consented remotely. A total of 2,659 patients were randomized: 1,366 received an ECG patch and instructions for self-application within two weeks (immediate group), and 1,293 received their patches four months later (delayed group). Additionally, 5,318 matched observational controls who were eligible for the study but not contacted for participation in the randomized trial were identified, two for each patient randomized.

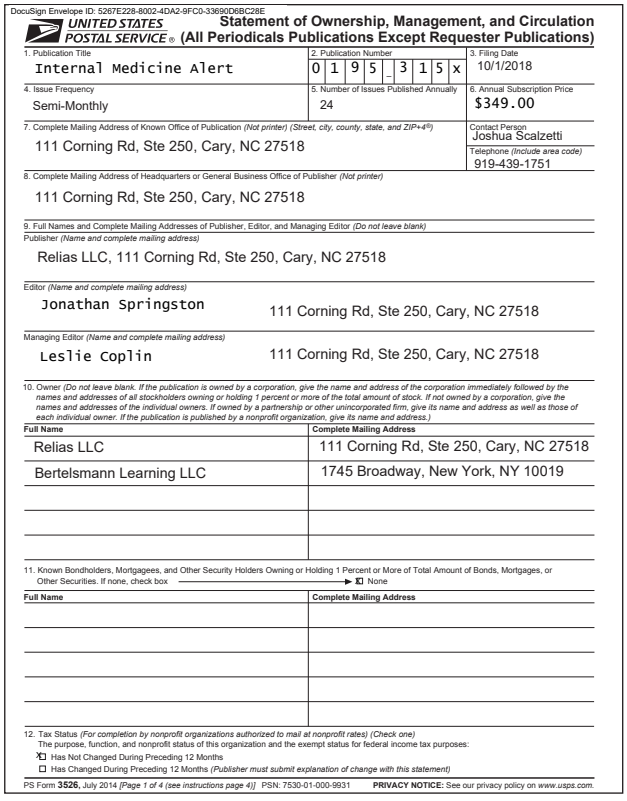
The primary endpoint in the intention-to-treat analysis of randomized patients was incidence of newly diagnosed AF (defined as ≥ 30 seconds of AF, flutter detected by device, or a new clinical diagnosis recorded in claims data at the end of the initial four-month monitoring period). In the immediate monitoring group, 908 of 1,366 participants wore an ECG patch, and incidence of new AF was 3.9%. In the delayed monitoring group, incidence of new AF was 0.9% in the first four months (before those participants received their patch). In the observational study with one-year follow-up, new AF was detected at a rate of 6.7 per 100 person-years in the actively monitored cohort (the two arms of the randomized trial) vs. 2.6 per 100 person-years in the matched observational controls.

Patients who were actively monitored were more likely to start both anticoagulation and antiarrhythmic medications. Further, there were more office visits as well as cardioversion and ablation procedures for these patients. However, the actively monitored group experienced a slightly lower incidence of hospitalizations or ED visits.

■ COMMENTARY

Improvements in digital technology for cardiac rhythm monitoring and AF diagnosis have made wearable devices that patients can use to send data to their physicians, or even self-diagnose, more accessible. Data from the mSToPS trial corroborate the work of other investigators who have evaluated more frequent or continuous monitoring and found a higher incidence of AF than would have been realized otherwise, including the REHEARSE-AF and CRYSTAL-AF studies. Uniquely, patients in the mSToPS trial were approached mostly via email, consented remotely, and applied and removed their own monitoring devices. In an ongoing trial, researchers are enrolling patients to use Apple Watch-based photoplethysmography to monitor for AF.

The increased rate of AF detection is not surprising. However, the absolute difference in detection rates between those monitored (for a median total monitoring time of about 25 days over a four-month period) and those not monitored still is impressive (considering 458 of 1,366 patients randomized to immediate monitoring never wore a patch). Also unsurprising is the resultant increase in healthcare resource use in the actively monitored cohort, with an increase in office visits, more prescriptions for anticoagulation therapy, and additional cardioversions and ablation procedures. The results may not be completely generalizable to a broader population. Patients who were invited to participate and enrolled were more likely to have been invited by email rather than direct mail, were slightly younger, more often male, and exhibited less hypertension and diabetes but more obesity and sleep apnea than those who declined. Additionally, patients who participated in randomization but never wore a monitor had some different characteristics than those who wore the patch. The larger question raised is whether more aggressive screening for AF in asymptomatic patients will translate to real long-term health benefits, and at what cost. The primary goal of detection for many patients would be stroke prevention via anticoagulation, but such a benefit has not yet been demonstrated. Additionally, more anticoagulation inevitably will lead to more bleeding events. The recently published NAVIGATE ESUS study ended early because patients empirically anticoagulated after a presumed embolic stroke without a clear source experienced more bleeding events and no apparent change in recurrent stroke risk at 11 months' follow-up. There are secondary benefits to earlier AF detection, such as a higher likelihood of aggressive risk factor modification, but also other ill effects, such as anxiety for some and complications of therapy for others.



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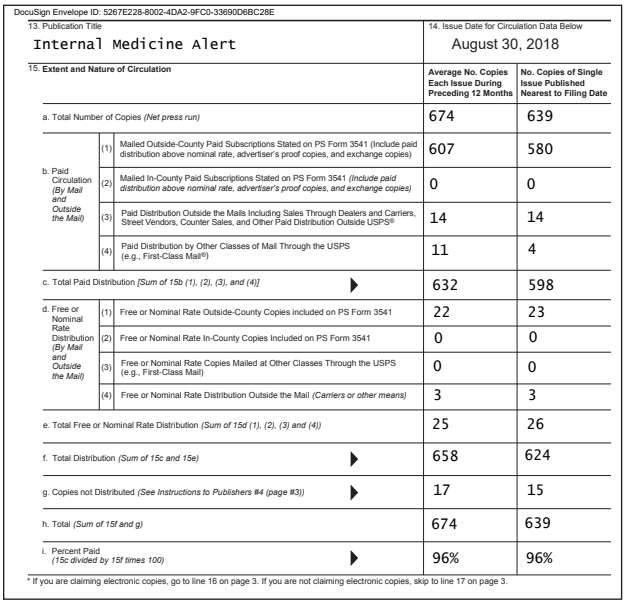

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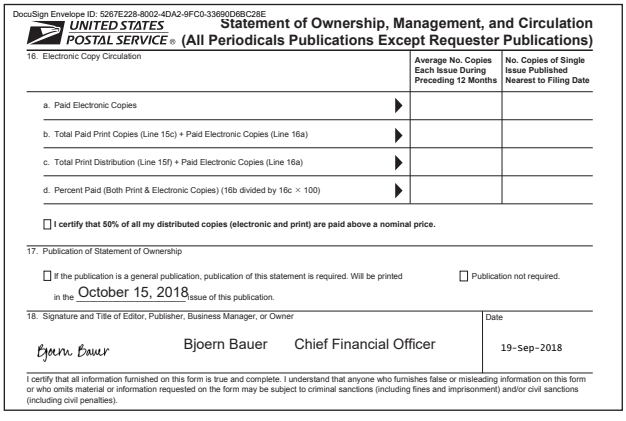

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Whether patients should screen and diagnose themselves with AF is the subject of active debate in the cardiology and EP communities. However, one thing is certain: Our methods for educating patients about AF and all the potential benefits and risks of early diagnosis and treatment must evolve at the same pace as the technology for detection. ■

PHARMACOLOGY UPDATE

Eravacycline Injection (Xerava)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new parenteral, broad-spectrum antibiotic in the tetracycline class for the treatment of complicated intra-abdominal infections (cIAI). Eravacycline is a synthetic fluorocycline that is chemically similar to tigecycline. It received a qualified infectious disease product designation and priority review. It is marketed as Xerava.

INDICATIONS

Eravacycline is indicated for patients ≥ 18 years of age to treat cIAI caused by the following: *Bacteroides* species, *Clostridium perfringens*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Escherichia coli*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus anginosus* group, and *Parabacteroides distasonis*.[1] Eravacycline should be used for infections that are proven or strongly suspected to be caused by susceptible microorganisms.[1] Because of inadequate efficacy, eravacycline is not indicated for the treatment of complicated urinary tract infection.[1,2]

DOSAGE

The recommended dose is 1 mg/kg by IV infusion (over 30 minutes) every 12 hours for four to 14 days.[1] For patients with severe hepatic impairment, the dose is 1 mg/kg every 12 hours on day 1 and 1 mg/kg every 24 hours from day 2 for the duration. For patients on a concomitant strong cytochrome P450 isoenzyme 3A inducer, the dose is 1.5 mg/kg.

POTENTIAL ADVANTAGES

Eravacycline offers a treatment option against multidrug-resistant bacterial infections, including extended-spectrum beta-lactamase and carbapenemase-producing Enterobacteriaceae, methicillin-resistant *S. aureus*, and vancomycin-resistant Enterococci.[3-5] Generally, eravacycline exhibits greater in vitro activity against gram-positive and gram-negative organisms compared to tigecycline.[3]

POTENTIAL DISADVANTAGES

In general, eravacycline is bacteriostatic against gram-positive bacterial and only bactericidal at relatively high concentrations against certain strains of *E. coli* and *Klebsiella pneumoniae*.[1,3] It is not active against *Pseudomonas aeruginosa*. Some beta-lactamase-producing isolates may confer resistance to eravacycline.[1,3] The frequency of adverse reactions (vs. comparators) was infusion site reaction (7.7% vs. 1.9%) and nausea (6.5% vs. 0.6%).[1] Life-threatening hypersensitivity (i.e., anaphylaxis) has been reported. Patients with known hypersensitivity to tetracycline should avoid eravacycline. Adverse reactions similar to other tetracycline classes of drugs may occur and may include photosensitivity, pseudotumor cerebri, and antianabolic actions. Use during pregnancy may cause reversible inhibition of bone growth, tooth discoloration, and enamel hypoplasia in the fetus.

COMMENTS

The efficacy of eravacycline was evaluated in two Phase III, randomized, double-blind, active-controlled trials in subjects with cIAI.[1,6] Acceptable diagnoses for cIAI include appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis.[1] In trial 1, subjects were randomized to eravacycline (1 mg/kg every 12 hours; n = 220) or ertapenem (1 g every 24 hours; n = 226). In trial 2, subjects were randomized to eravacycline (1 mg/kg every 12 hours; n = 195) or meropenem (1 g every eight hours; n = 205). The analysis was based on the microbiologic intent-to-treat population, which included all patients who presented with at least one baseline intra-abdominal pathogen. Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the index infection at the test-of-cure visit, which occurred 25-31 days after randomization. Clinical cure rates were 86.8% for eravacycline vs. 87.6% for ertapenem in trial 1 and 90.8% vs. 91.2% for meropenem in trial 2. Both studies met the statistical criteria for noninferiority (lower limit of -10%). Eravacycline did not demonstrate noninferiority to levofloxacin for the treatment of complicated urinary tract infections and is not approved for this indication currently.[1,2]

CLINICAL IMPLICATIONS

cIAI is a polymicrobial, heterogenous infection generally involving gram-positive cocci, gram-negative bacilli, and

anaerobic bacteria. It may be community-acquired or healthcare-associated.[7] cIAI is the second-leading cause of infection-related mortality in ICUs.[8] In previous guidelines, the recommendation for single-agent empiric antimicrobial treatment included cefoxitin, ertapenem, tigecycline, meropenem, or a combination of a cephalosporin and metronidazole.[7] However, multidrug-resistant bacteria have emerged, particularly with *E. coli* and *K. pneumoniae*.[4] Eravacycline is one of the newer agents in development that has received FDA approval and has shown activity against multidrug-resistant bacteria. It should be reserved for infections that are proven or strongly suspected to be caused by susceptible bacteria.[1] The cost for eravacycline was not available at the time of this review. ■

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CME QUESTIONS

1. Which medication would be most appropriate for a 52-year-old male with a medical history that included significant hypertension and atrial fibrillation?
a. Aspirin 81 mg once daily
b. Rivaroxaban 20 mg once daily
c. Warfarin titrated to an international normalized ratio of 2-3
d. Clopidogrel 75 mg and aspirin 81 mg once daily

2. Which statement is true based on the findings in the Waterer et al study regarding community-acquired pneumonia (CAP)?
a. Adults hospitalized with CAP have a mortality rate of 23%.
b. Most in-hospital deaths among patients admitted for CAP do not appear preventable with improvements in inpatient care.
c. Most inpatient CAP deaths are among adults < 65 years of age.
d. Most inpatient CAP deaths occurred after 14 days.

3. A large study comparing a new self-applied patch for atrial fibrillation detection to controls showed:
a. lower stroke rates.
b. less drug therapy.
c. more atrial fibrillation detected.
d. fewer office visits.

CME OBJECTIVES

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

Internal Medicine [ALERT]

ECG Review

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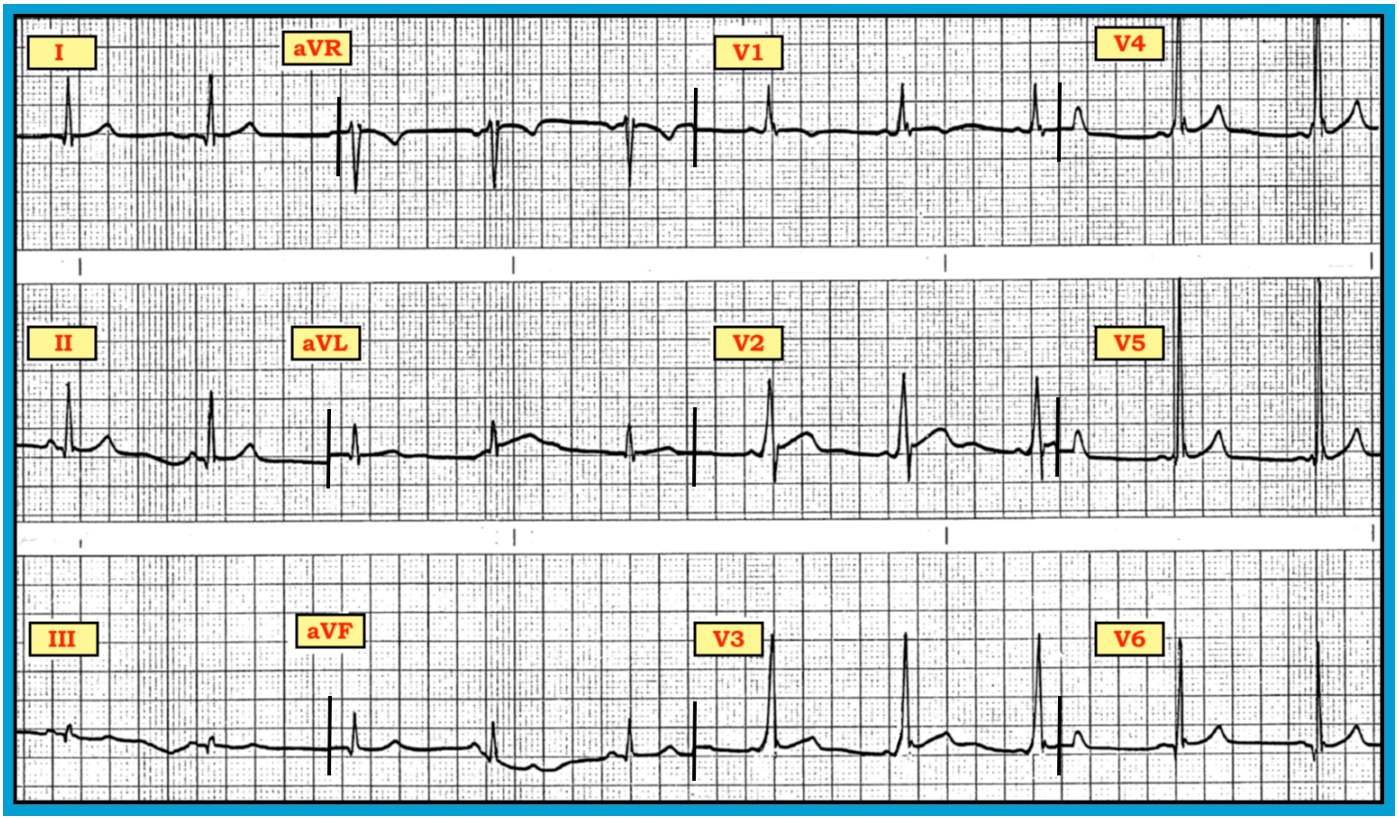
Dr. Grauer reports no financial relationships relevant to this field of study.

Biventricular Hypertrophy in an Asymptomatic Patient?

As part of a pre-employment physical, the ECG in the figure below was obtained from an asymptomatic, otherwise healthy 39-year-old male. How might one interpret this ECG? Is there right ventricular hypertrophy (RVH)? What about left ventricular hypertrophy (LVH)?



The rhythm is sinus at ~60-65/minute. But the PR interval appears short (i.e., < 0.12 seconds). When studying QRS complex in all 12 leads, one sees there is a slight QRS widening (especially in leads V2 and V3). There could be some slurring of the initial part of the QRS complex in a few precordial leads. Thus, this patient has Wolff-Parkinson-White (WPW) syndrome.

Usually, WPW is easily recognized on ECG when conduction completely uses the accessory pathway (AP). One should look for delta waves, a short PR interval, and QRS widening — even when conduction is over entirely of the AP (delta waves will not always be visible in every lead). Further, delta waves may appear and disappear, since conduction over the AP may be intermittent. Sometimes, conduction may happen at the same time over the AP *and* the normal. If this occurs, the WPW ECG characteristics may appear subtle because the contribution from conduction over the normal AV nodal pathway may predominate (and mask) ECG features of pre-excitation. Because of less-than-complete pre-excitation, it would be easy to overlook WPW in this case. Other than a slightly shortened PR interval, not much appears abnormal in the limb leads. One observes definite delta waves in leads V1, V2, V3, and V4 only. WPW may mimic other ECG conditions. Thus, the slightly widened and upright QRS complex in V1 mimics right bundle branch block and RVH. The markedly increased QRS amplitude observed in V5 imitates LVH. Still, one cannot diagnose these conditions on ECG because the patient has WPW. When viewing this ECG, we cannot determine if ventricular enlargement or bundle branch block also exist.

For more information about and further discussion on this case, please visit: https://bit.ly/2MKPl8U.