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INSIDE

Early Surgery for Infective Endocarditis Decreases Risk of Embolization, Mortality

ABSTRACT & COMMENTARY

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

This article originally appeared in the August 2012 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 this randomized study, patients with left-sided infective endocarditis and large vegetations who underwent valve replacement surgery within 48 hours of randomization had lower rates of embolic events and death from any cause after 6 months compared to those who underwent surgery later.*

Source: Kang D-Y, et al. Early Surgery versus Conventional Treatment for Infective Endocarditis. *N Engl J Med* 2012;366:2466-2473.

Infective endocarditis (IE) continues to be a serious illness with high morbidity and mortality despite modern therapies. Current guidelines from the American Heart Association state that the benefit from surgical intervention is greatest in the early phases of IE, when embolic rates are highest and other predictors of a complicated course are present.[1] Kang and colleagues conducted a prospective, randomized, controlled trial in patients 18 years of age and older

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with left-sided, native-valve IE and a high risk of embolization. Eligible patients received a diagnosis of IE by the modified Duke criteria, had severe mitral or aortic valve disease and a vegetation ≥ 10 mm in diameter. All patients underwent transesophageal echocardiography and computed tomography of the brain and abdomen to evaluate for embolism. They were assigned in a 1:1 ratio to the early-surgery group (valve replacement within 48 hours after randomization) or the conventional treatment group (surgery performed only if complications developed during medical therapy or if symptoms persisted after completion of antibiotic therapy). Between September 2006 and March 2011, 37 patients were assigned to early surgery and 39 to conventional therapy. The primary end point was in-hospital death or clinical embolic events within 6 weeks of randomization. Secondary end points at 6 months of follow-up were death from any cause, embolic events, recurrence of IE, and hospitalization due to congestive heart failure (CHF).

The investigators found that the most common pathogens were viridans streptococci (30% of patients), other streptococci (in 30%), and *Staphylococcus aureus* (in 11%). There were no significant differences in antibiotic therapy between the two groups. The median time from randomization to surgery in the early-surgery group was 24 hours (range 7 to 45 hours). The primary end point of in-hospital death or embolic events within the first 6 weeks occurred in one patient (3%) in the early-surgery group, compared to 9 (23%) in the conventional-treatment group (hazard ratio, 0.10; 95% confidence interval 0.01 to 0.82; P=0.03). At 6 weeks after randomization, the rate of embolization in the early-surgery group was 0% compared to 21% in the conventional-treatment group (P=0.005). Among the 11 patients in the conventional-treatment group who were discharged without having surgery, 1 (3%) died suddenly, 7 (18%) had symptoms related to severe valve disease or recurrence of IE, and 3 (8%) had no symptoms or embolic events. At 6 months the rate of death from any cause, embolic events, recurrence of IE, or repeat hospitalization due to the development of CHF was 3% in the early-surgery group, compared to 28% in the conventional-treatment group (hazard ratio, 0.08; 95% confidence interval, 0.01 to 0.65; P=0.02). There was no significant difference between the groups in all-cause mortality at 6 months (3% and 5%, P=0.59).

There were several limitations to the study. One was the overall number of patients in the two groups was small. This was likely a consequence of the exclusion criteria chosen by the authors: patients with strokes, IE involving prosthetic valves, or aortic abscess. Another limitation was the low incidence of *S. aureus* IE, which was lower than previously reported.[2] The rate of death within 30 days after surgery was low and the patients had a low operative risk. This implies that the results of the study may not be applicable to low-volume medical centers or to patients with a high operative risk. The study was conducted at two medical centers and the researchers did not analyze outcomes according to each participating center because of large differences in numbers of patients enrolled at each site. Follow-up imaging studies to detect subclinical embolic events were not done.

■ COMMENTARY

The decision about when a patient should undergo surgical intervention for IE is often challenging. The current IE guidelines strongly recommend urgent surgery for patients with CHF due to valvular regurgitation.[1] However, in patients with large vegetations and valve dysfunction but not CHF the guidance is less clear. The study by Kang and colleagues has provided valuable new data on this clinical conundrum. Their findings are very convincing to support the argument in favor of early surgery for patients with large vegetations and valvular dysfunction without overt CHF. As pointed out in an accompanying editorial, the benefits of timely intervention outweighed the additional risk of surgery in patients with active infection.[3] Adequate debridement during surgery and optimal antibiotic selection based on culture data is also paramount to achieve successful outcomes.

It was surprising that *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), was not a more common etiology of IE in the study. MRSA is highly pathogenic due to a multitude of virulence factors and is a frequent cause of embolic disease.[4] It is unclear if the outcomes would have been different if more patients had *S. aureus* IE. Additional research to investigate this issue, especially in areas where MRSA is highly prevalent, is warranted.

The authors reported the time from randomization to sur-

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

gery but not from diagnosis to surgery. Presumably these times were similar in most cases but this was not explicitly stated in the study. Moreover, the interval from onset of symptoms to surgery was not mentioned.

Despite its limitations, this study provides compelling evidence to support surgery in the first 48 hours for patients with left-sided IE, large vegetations and evidence of valvular dysfunction. IE is a perilous condition with a high risk of embolic events. The study by Kang and colleagues is important and will hopefully lead to improved clinical outcomes for patients. Future studies to replicate these data, especially with larger numbers of participants and high risk patients, are necessary to further elucidate the optimal timing of surgery in IE. ■

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Survival After Out-of-Hospital Cardiac Arrest

ABSTRACT & COMMENTARY

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This article originally appeared in the August 2012 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, and peer reviewed by Ethan Weiss, MD. Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and Dr. Weiss is 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: Dumas, F, et al. Long-term prognosis following resuscitation from out of hospital cardiac arrest: Role of percutaneous coronary intervention and therapeutic hypothermia. *J Am Coll Cardiol* 2012;60:21-27.

In this paper, the authors reviewed long-term survival data from a large population of out-of-hospital cardiac arrest patients who were discharged alive after their arrest. All patients who have a cardiac arrest in Seattle and King County, Washington, are entered into a registry organized to follow the Utstein guidelines for reporting cardiac arrest. During the 8-year period from 2001 to 2009, the survival rate to hospital discharge was 16.8% (1101 of 5958 adult patients) after EMS treated nontraumatic out-of-hospital cardiac arrest. Factors associated with long-term survival after hospital discharge were then examined. The factors analyzed included the use of therapeutic hypothermia, percutaneous coronary interventions (PCI), implantable cardioverter defibrillators (ICDs), neurologic status upon hospital arrival, and ST-segment elevation on the initial hospital ECG. In this cohort of survivors to hospital discharge, 38% received a PCI during the hospitalization after arrest. Six percent were conscious at hospital admission and were not candidates for therapeutic hypothermia. Among the 941 patients who were unconscious at hospital admission, 245 (26%) received therapeutic hypothermia. Both PCI and therapeutic hypothermia were employed in 9.9% of the cohort, with 80% of the PCIs occurring within 6 hours of hospital arrival. Of those who received PCI within 6 hours, 71% had evidence of ST-segment elevation on the initial hospital ECG.

The median age in the group was 61 and two-thirds of the patients were male. Eighty percent had a cardiac etiology for their arrest and almost 70% had an initial shockable rhythm detected. Patients who received PCI were younger and were more likely to have the following characteristics: male gender, an arrest due to a cardiac etiology, a witnessed arrest in a public location, and bystander CPR. After hospital discharge, 348 of the 1101 patients died. Life table analysis gave survival estimates of 87% at 6 months, 82% at 1 year, and 64% at 5 years. Both PCI and therapeutic hypothermia were associated with favorable effects on mortality. Patients who received both PCI and therapeutic hypothermia had the highest survival estimates at both 1 and 5 years. Cox regression analysis showed that PCI, therapeutic hypothermia, and ICD implantation were each independently associated with improved survival after discharge. The hazard ratios for risk of death were 0.46 for PCI and 0.70 for therapeutic hypothermia. The hazard ratio for death was lowest for those who received PCI during an ST segment elevation MI (0.41). A further analysis using a nested cohort pairing for each intervention showed similar favorable hazard ratios associated with both therapeutic hypothermia and PCI.

The authors conclude that in this observational analysis, both PCI and therapeutic hypothermia produced survival benefits among patients who survived to hospital discharge. Since only patients who were discharged from the hospital were analyzed in this study, improved in-hospital survival could not be assessed but has been demonstrated in other reports.

■ **COMMENTARY**

This report from a large, well-organized registry of out-of-hospital cardiac arrest victims provides further data to support the routine use of coronary angiography followed, when indicated, by PCI and therapeutic hypothermia in resuscitated cardiac arrest victims admitted to the hospital. The largest benefit shown was for ST elevation patients and this report confirms that both PCI and therapeutic hypothermia can and should be used in these patients. In patients without STEMI, the best timing for coronary angiography remains controversial, but certainly detecting and treating high-grade coronary lesions where present should be considered at some time during the hospital stay.

Recently, some hospitals have been cited by state boards or other groups for increased adjusted mortality rates among PCI patients. In several cases, most of the PCI-related deaths occurred in patients who presented in shock or after a resuscitated cardiac arrest. The risk-adjustment schemes did not fully account for the much higher than expected mortality in such patients. Therefore, the American Heart Association has recommended that patients in shock or after arrest be separately classified from other PCI patients when data are reported. The data in this paper support this idea since we should not punish hospitals that accept the burden of treating these very high-risk patients. ■

Rapid Rule Out for Patients with Chest Pain

ABSTRACT & COMMENTARY

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Dr. Boyle reports no financial relationships relevant to this field of study. This article originally appeared in the August 2012 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, and peer reviewed by Ethan Weiss, MD. Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and Dr. Weiss is 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: Than M, et al. 2-hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: The ADAPT trial. *J Am Coll Cardiol* 2012;59:2091-2098.

Chest pain presentations to the emergency department (ED) are common and very costly to the health care system. Although the event rates are low in patients with a low clinical risk profile, the price of a missed diagnosis is high. Some low-risk patients who are discharged from the ED may suffer a myocardial infarction (MI) and potentially even die. Our ability to predict who will go on to suffer an acute coronary syndrome (ACS) is imperfect. Thus, many patients are unnecessarily admitted to the hospital for observation. A more rapid means to assess low-risk chest pain (i.e., rule out MI) in the ED may facilitate earlier discharge and lead to substantial savings for the health care system.

Than and colleagues developed an accelerated diagnostic protocol (ADP) to rapidly rule out MI in low-risk patients presenting to the emergency room with chest pain. Their aim is to facilitate early discharge from the ED in these patients, and the ADAPT (2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker) trial is a prospective, observational study performed at two urban EDs. Their protocol identified low-risk chest pain patients as those with a Trials In Myocardial Infarction (TIMI) risk score of 0, no ischemic ECG changes, and negative cardiac troponin I (cTnI) upon arrival and at 2 hours. The TIMI risk score applies 1 point for each of the following parameters: age > 65 years, ≥ three cardiac risk factors, aspirin use in the preceding 7 days, known coronary stenosis ≥ 50%, ≥ two episodes of chest pain in the preceding 24 hours or ongoing pain, ST segment changes on the ECG, and elevation of biomarkers. All patients had cTnI drawn at 0 and 2 hours after arrival. Importantly, the 2-hour cTnI was not communicated to the physicians, so usual care was performed (which usually entailed a 6-12 hour cTnI measurement). The primary endpoint of the study was major adverse cardiac events (MACE) occurring within 30 days of presentation (including during the initial hospitalization). MACE included: death (unless clearly non-

cardiac), MI, cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia needing intervention, and high-degree atrioventricular block needing intervention. Follow-up was by review of hospital records, national death index, and telephone contact.

Of the total 1975 patients enrolled, 302 (15.3%) had a MACE within 30 days. The ADP classified 392 patients (20%) as low risk. No patients were lost to follow-up. One (0.25%) of these patients had a MACE, giving the ADP a sensitivity of 99.7% (95% confidence interval [CI]: 98.1% to 99.9%), negative-predictive value of 99.7% (95% CI: 98.6% to 100.0%), specificity of 23.4% (95% CI: 21.4% to 25.4%), and positive-predictive value of 19.0% (95% CI: 17.2% to 21.0%). Because the results of the cTnI were not communicated to the treating physician, most ADP-negative patients had further investigations (74.1%), and therapeutic (18.3%) or procedural (2.0%) interventions during the initial hospital attendance and/or 30-day follow-up. The authors performed a post-hoc analysis to determine the sensitivity and specificity of each parameter of the ADP using combinations of two parameters. They found that using all three parameters of the ADP (TIMI risk score of 0, non-ischemic ECG, and negative cTnI) performed best.

The authors conclude that when using the ADP, a large group of patients was successfully identified as having low short-term risk of a MACE and therefore suitable for rapid discharge from the ED with early follow-up. This approach could decrease the observation period required for some patients with chest pain.

■ COMMENTARY

Any strategy that can safely facilitate the more rapid discharge of patients from the ED would be most welcome. This study from Than and colleagues represents a step in that direction. The identification of low-risk patients who may be suitable for early discharge by simple clinical risk features, ECG, and a 2-hour cTnI measurement may help alleviate ED crowding. The rate of MACE in their low-risk cohort (one patient with a missed MI; 0.25%) was low, and is in the range that many ED physicians would call "acceptable." However, exactly what one considers an acceptable rate of missed MI remains the subject of considerable debate.

This study has several strengths that should be noted. First, they used a current fourth-generation troponin assay that is similar to those widely used in the United States today. Second, this was a prospective, two-center study performed in two countries (but not in the United States). These features add weight to the conclusions that can be drawn. However, several limitations should also be noted. First, by not allowing the physicians access to the 2-hour troponin result, these patients were not actually discharged early. They all underwent 6- to 12-hour follow-up troponin and the majority underwent stress testing or invasive treatments. The MACE endpoint included emergency revascularization, but not elective treatment/revascularization. It is possible that some of the treatments received may have reduced the MACE rate. I would like to have seen data on what treatments these patients received. Second, the patients were predominantly Caucasian males, so the results may not be generalizable to women and non-Caucasian populations. This study is exciting in that it may lead to earlier discharge of these low-risk patients from the ED. However, until the strategy of discharge is actually tested prospectively, this study should be considered hypothesis generating rather than practice changing.

Where this approach will fit in the evolving world of chest pain assessment is not clear. Computed tomography coronary angiography is increasingly being used to rule out MI in low-intermediate risk groups. In addition, highly sensitive troponin assays are emerging and show potential to diagnose or rule out MI earlier, albeit with a trade-off of more "false" positives. Dedicated chest pain centers with after hours stress testing facilities are appearing. Future studies will define the best use of all of these new approaches, and will hopefully reduce ED crowding and the economic burden of chest pain presentations on the health care system. ■

Invasive or Conservative Strategy in Diabetics with ACS?

ABSTRACT & COMMENTARY

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Dr. Boyle reports no financial relationships relevant to this field of study. This article originally appeared in the August 2012 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, and peer reviewed by Ethan Weiss, MD. Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and Dr. Weiss is As-*

sistant 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: O'Donoghue ML, et al. An invasive or conservative strategy in patients with diabetes mellitus and non–ST-segment elevation acute coronary syndromes. A collaborative meta-analysis of randomized trials. *J Am Coll Cardiol* 2012;60:106-111.

Patients with diabetes mellitus (DM) are at increased risk of developing acute coronary syndromes (ACS). Furthermore, after hospitalization with ACS, patients with DM are at increased risk of suffering repeat hospitalization for ACS. In recent years, a number of trials have tested the strategy of routine early invasive approach (i.e., diagnostic angiography with a view to revascularization) vs an early conservative strategy (i.e., medical management with coronary angiography only performed in cases of refractory ischemia). The invasive strategy is generally preferable in patients at high risk of clinical events, and this is reflected in the ACC/AHA guidelines. Diabetes is known to confer an increased risk of clinical events. Whether patients with DM and ACS should routinely undergo an invasive strategy is not known. O'Donoghue and colleagues performed a collaborative meta-analysis of nine clinical trials that tested invasive vs conservative strategies in patients with ACS, comparing outcomes between diabetic and non-diabetic patients. The primary endpoint was a composite of death, myocardial infarction (MI), and repeat hospitalization for ACS.

The authors studied 9904 patients in nine trials, of whom 18.2% were diabetic. Patients with DM tended to be older and were more likely to be female, have hypertension, hyperlipidemia, and a history of MI. In addition, patients with DM had more extensive coronary artery disease and were more likely to undergo coronary artery bypass graft (CABG) surgery than non-diabetics. Diabetics had higher rates of death (9.3% vs 3.2%; $P < 0.001$), nonfatal MI (11.3% vs 7.1%; $P < 0.001$), and rehospitalization with ACS (18.1% vs 13.0%; $P < 0.001$) compared with non-diabetic patients. The primary endpoint was reduced by an invasive strategy to a similar extent in patients with DM (relative risk [RR] 0.87; 95% confidence interval [CI] 0.73-1.03) and those without (RR 0.86; 95% CI, 0.70-1.06). Randomization to an invasive strategy reduced non-fatal MI in diabetic patients (RR 0.71; 95% CI, 0.55-0.92) but not in non-diabetics (RR 0.98; 95% CI, 0.74-1.29). The absolute risk reduction in MI with an invasive strategy was greater in diabetic than non-diabetic patients (absolute risk reduction: 3.7% vs 0.1%). There were no differences in death or stroke between diabetics and non-diabetics. Interestingly, patients with DM received a benefit from an invasive strategy regardless of whether they had positive biomarkers. In contrast, non-diabetics only received benefit from an invasive strategy if they were biomarker positive.

The authors conclude that an early invasive strategy yielded similar RR reductions in overall cardiovascular events in diabetic and non-diabetic patients. However, an invasive strategy appeared to reduce recurrent non-fatal MI to a greater extent in diabetic patients. These data support the updated guidelines that recommend an invasive strategy for patients with DM and non-ST-segment elevation ACS.

■ COMMENTARY

This meta-analysis confirms that diabetics have a higher risk of cardiac events than non-diabetics. It also demonstrates that diabetics and non-diabetics who present with ACS receive a similar benefit from an early invasive strategy. This confirms the current ACC/AHA guidelines that suggest markers of increased risk in patients with ACS should include the presence of diabetes.

Several limitations of this study should be mentioned. First, meta-analyses are subject to biases including which studies were included, selection bias, and individual study protocol differences that are not mentioned. Second, diabetics were more often treated with CABG than non-diabetics (31% vs 25%) and we are not told whether the outcomes were influenced by the use of CABG instead of PCI. It is possible that the higher rates of CABG in diabetics resulted in superior clinical outcomes. Third, this meta-analysis was a study-level rather than a patient-level meta-analysis. Thus, individual covariates were not examined.

Importantly, many of the studies included in this meta-analysis were in the era of bare-metal stents (BMS). Drug-eluting stents (DES), particularly the newest generation of DES, lead to better outcomes in diabetics compared to BMS. Use of DES may result in an even greater magnitude of improvement in outcomes in diabetic patients who undergo invasive treatment. Patients with ACS should be risk-stratified and higher-risk patients considered for an invasive strategy. Diabetic patients should be considered in this high-risk group. ■

Intravenous Thrombolysis Is Relatively Safe and Effective in Elderly Patients Up to 6 Hours After Symptom Onset

STROKE ALERT

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Matthew Fink, MD, is a retained consultant for MAQUET.
This article originally appeared in the August 2012 issue of Neurology Alert. *It was peer reviewed by M. Flint Beal, MD. Dr. Beal is Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Beal reports no financial relationships relevant to this field of study.*

Source: The IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischemic stroke (the third international stroke trial [IST-3]): A randomized controlled trial. *Lancet* 2012;370: 2352-2363.

After results of the pivotal NINDS intravenous thrombolysis (IV rtPA) trial were published in 1995, there has been a gradual extension of the time window from 3 hours to 4.5 hours, based on additional trials (ECASS II and III). However, the very elderly (> 80 years of age) have been largely excluded from studies and the value of IV rtPA in this group, especially for an extended time window (4.5 to 6 hours), was uncertain. IST-3 was organized as an open-label, randomized trial to include those patients who currently did not have a clearly approved indication for IV rtPA (age > 80 and time > 4.5 hours) with a primary outcome measure of the proportion of patients alive and independent at 6 months.

The study included 3035 patients in 156 hospitals in 12 countries, and 1617 (53%) were > 80 years of age. At 6 months, 554 (37%) patients in the rtPA group were alive and independent compared to 534 (35%) in the control group (OR = 1.13, 95% confidence interval [CI] 0.95-1.35, P = 0.181). However, the rtPA group had a higher rate of early complications and early mortality. More deaths occurred within 7 days in the rtPA group, and symptomatic intracranial hemorrhage within 7 days occurred in 7% of rtPA patients vs 1% in controls. Despite these early hazards, the 6-month outcomes favored the administration of rtPA. ■

Meta-analysis of All Randomized Trials Supports the Benefits of Intravenous Thrombolysis for All Patients Up to 6 Hours

STROKE ALERT

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This article originally appeared in the August 2012 issue of Neurology Alert. *It was peer reviewed by M. Flint Beal, MD. Dr. Beal is Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Beal reports no financial relationships relevant to this field of study.*

Source: Wardlaw JM, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: An updated systematic review and meta-analysis. *Lancet* 2012;379:2364-2372.

The recently published IST-3 trial has stimulated great interest in the expanded use of intravenous thrombolysis (IV rtPA). Wardlaw and colleagues assessed all of the evidence from published randomized trials for IV rtPA in acute ischemic stroke using a meta-analysis. They searched for all randomized trials of IV rtPA given within 6 hours of onset of ischemic stroke, using prespecified outcomes at 7 days and at final follow-up.

In 12 trials that included 7012 patients, IV rtPA given within 6 hours significantly increased the odds of being alive and independent at final follow-up (46.3% vs 42.1%, OR = 1.17, 95% CI 1.06-1.29; P = 0.001). The benefit of IV rtPA was greatest in patients treated within 3 hours (40.7% vs 31.7%). However, the number of deaths within 7 days was increased in the treated group (8.9% vs 6.4%), but by the time of final follow-up, this excess was not significant. Symptomatic intracranial hemorrhage accounted for most of the early excess deaths (7.7% vs 1.8%). Patients older than 80 years of age achieved similar benefit, particularly when treated early. The preponderance of evidence supports the use of IV rtPA up to 6 hours from the onset of acute ischemic stroke. ■

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 randomized trial by Kang et al., what patient group benefitted from early surgery for infective endocarditis?

a. Patients with left-sided endocarditis, large vegetations, and significant valvular dysfunction.

b. Patients with right-sided endocarditis, small vegetations, and minimal valvular dysfunction.

c. Patients with prosthetic valve endocarditis, large vegetations, and no valvular abscesses.

d. All patient groups with infective endocarditis.

2. Which of the following statements most closely matches the findings in the meta-analysis of recombinant tissue plasminogen activator (rtPA) for stroke by Wardlaw and colleagues?

a. The benefit of rtPA was only seen in patients under the age of 80 years presenting within 3 hours of onset of stroke symptoms.

b. The benefit of rtPA was only seen in patients under the age of 80 years presenting within 4.5 hours of onset of stroke symptoms

c. The benefit of rtPA may extend to patients over the age of 80 years but only those presenting within 3 hours of onset of stroke symptoms.

d. The benefit of rtPA was seen in patients presenting within 6 hours of onset of stroke symptoms, including in those patients over 80 years of age.

3. Based on the study by Dumas et al., what factors were independent predictors of long-term survival after out-of-hospital cardiac arrest?

a. Therapeutic hypothermia.

b. ICD implantation.

c. Percutaneous coronary intervention.

d. All of the above.

CME Instructions

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

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Risk for Zoster from the Vaccine in Immunosuppressed Persons

Source: Zhang J, et al. *JAMA* 2012;308: 43-49.

The prevailing wisdom suggests that because herpes zoster vaccine (ZOS) is a live virus, it should not be administered to persons receiving immunosuppressive treatments, such as biologic agents or methotrexate for rheumatoid arthritis, or chronic prednisone therapy of 20 mg/d or more. The concern is that instead of mounting an immune response to the vaccine, vaccinees might actually experience a case of shingles as a result of the vaccine.

To examine the real-life risk of an acute zoster infection after ZOS, a retrospective analysis was performed on a large Medicare database (n = 463,541) of persons with a diagnosis of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease. Any one of these disorders would be commonly treated with immunosuppressive agents, corticosteroids, or both.

The analysis looked at the number of cases of shingles within 42 days of ZOS, anticipating that if the live virus vaccine had induced shingles, it should certainly have happened within that 6-week window after vaccination.

No increased incidence of shingles was seen in ZOS recipients, even in patients on biologics. Indeed, ZOS was associated with a 39% lower risk of shingles during the 42-day window of observation, and a reduced risk during the subsequent 2 years (median) of follow-up. ZOS appears to be beneficial even in immunocompromised individuals, and the authors challenge the propriety of current recommendations that advise against ZOS administration in such populations. ■

Cerebral Aneurysms: What's in Your Patient's Future?

Source: UCAS Japan Investigators. *N Engl J Med* 2012;366:2474-2482.

The UCAS (unruptured cerebral aneurysm) Japan study began enrolling patients with incidentally discovered cerebral aneurysms (CRAs) for an observational study in 2001. The primary purpose of the study was to better delineate the natural history of incidentally discovered CRAs (as opposed to discovery through neurologic signs or symptoms). Prior to this trial, it had been generally recognized that CRAs < 7 mm rarely rupture, and that posterior circulation CRAs have a greater risk than anterior.

This prospective cohort study included patients (n = 6413) with incidentally discovered CRA and minimal, if any, disability. Subjects were followed for up to 8 years. During this interval, the annual rate of CRA rupture was approximately 1%. When rupture did occur, it was fatal in 35% of cases, or led to moderate-severe disability in another 29%.

The most important predictive factors for rupture were size of the CRA, age, and gender (females are at greater risk). For example, when compared with lesions < 7 mm, a 7-9 mm lesion had a three-fold increase of rupture, and a lesion > 10 mm had a nine-fold increased risk. Risk in women was 1½ times as great as men, and persons over age 70 were 21% more likely to experience aneurysm rupture. Because the entire population of enrollees was Japanese, the generalizability of these results may have limitations, but nonetheless provide perhaps the most accurate mapping of risk factors for rupture of CRAs. ■

Elucidating the 'Best' Interval for Bone Density Screening in Osteoporosis

Source: Yu EW, Finkelstein JS. *JAMA* 2012;307:2591-2592.

Once a baseline bone mineral density (BMD) has been obtained, it is unclear when the study should be repeated. For one thing, the literature suggests that only about 30% of bone strength may be attributable to bone density. Additionally, some of the interventional trials using bisphosphonates have found fracture reduction despite continuation of bone density *loss* over the first year or two of intervention. Finally, the rate at which BMD declines has been linked to the baseline BMD.

For instance, a study that looked at menopausal women (age > 67 years) for progression of BMD loss found some fairly startling results: It would take approximately 15 years for 10% of women with normal baseline BMD (T score < -1.5) to incur sufficient loss of BMD to cross the diagnostic threshold for osteoporosis (T score < -2.5). Similarly, for women with osteopenia (T score -1.5 to -2.0) at baseline, it would require 5 years for 10% of

them to progress to frank osteoporosis. At the greatest level of osteopenia (T score -2.0 to -2.5), progression to osteoporosis in 10% of women would be expected to occur within 1 year. These projections assume no addition of new risk factors known to accelerate bone loss.

Although it is tempting to get BMD more often, it may not be helpful. Although the data are sufficiently uncertain that the USPSTF has been unable to provide confirmation of a preferred schedule, Yu et al suggest following rescreening intervals for postmenopausal women: for women with normal BMD at baseline, 10 years; for women with mild osteopenia and low FRAX score at baseline, 5-10 years; for women with moderate osteopenia or FRAX score approaching treatment threshold, 2 years. ■

An Unexpected Connection Between PTSD, ACE Inhibitors, and ARBs

Source: Khoury NM, et al. *J Clin Psychiatry* 2012;73:849-855.

Several lines of evidence suggest that modulation of the renin-angiotensin-aldosterone system with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) might potentially have positive effects on post-traumatic stress disorder (PTSD). Preclinical data indicate favorable cerebral effects of ARBs, such as stress reduction and anxiolysis. Some ARB trials have reported positive effects on cognition, quality of life, and depression or anxiety.

Khoury et al performed a cross-sectional observational data analysis of PTSD patients (n = 505) comparing symptoms in those who were being treated with an ARB/ACE vs controls (no ARB/ACE treatment). Overall, PTSD symptom scores were almost 25% lower among patients treated with ACE or ARB therapy ($P = 0.04$).

The better symptom scores among PTSD patients treated with ARB or ACE therapy were not simply due to the fact that hypertension (which is more common in PTSD patients) was treated; no other antihypertensive medications (e.g., calcium channel blockers, diuretics, beta-blockers) were found to have similar favorable effects.

The mechanism through which ACE/ARB treatments impact PTSD is not well established, but may be through modulation of the noradrenergic system. ■

The Right Amount of Vitamin D to Prevent Fractures

Source: Bischoff-Ferrari HA, et al. *N Engl J Med* 2012;367:40-49.

Inclusion of vitamin D (VTD) in the regimen for fracture prevention is time honored and condoned by major guidelines. Intuitively, VTD should be helpful, but the analyses of data in reference to this topic are mixed. For instance, although one meta-analysis indicated an 18% reduction in hip fracture if a minimum of 482 IU/d VTD was prescribed, equally prominent data concluded that VTD alone was of *no benefit*. So, how about further investigation of the subject?

Bischoff-Ferrari et al performed an analysis on 11 double-blind, randomized, controlled trials of oral VTD supplementation (n = 31,022) seeking to determine if supplementation (with or without calcium) reduced hip fracture. According to their analysis, there was no statistically significant reduction in fracture risk in subjects assigned to VTD. Story over? Well, maybe not quite.

First, although hip fracture was not reduced, there was a marginally statistically significant 7% reduction of total non-vertebral fractures. Additionally, when analyzed from the viewpoint of the *actual intake* of VTD instead of what subjects were assigned to, the picture looks quite different. Specifically, subjects in the highest quartile of actual VTD intake (prescribed supplementation plus dietary intake) enjoyed a statistically significant 30% reduction in hip fracture. For the time being, at least 800 IU/d VTD supplementation is recommended in persons ≥ age 65. ■

Prevention of Diabetes

Source: Perreault L, et al. *Lancet* 2012; 379:2243-2251.

It appears that one's ounce of prevention may have to be weighed more carefully to attain the fullest pound of cure. Why? The answer lies in subgroup analysis of recent trials in diabetes prevention.

There have been many diabetes prevention trials, essentially all of which have been successful to a varying degree. Overall, diet and exercise appear to be as efficacious as any other intervention. Pharmacologically, numerous classes of agents have been successfully tried (metformin, thiazolidinedione, alpha-glucosidase inhibitor, etc.). What has been learned is that successful incorporation of diet/exercise or pharmacotherapy over a 4- to 6-year period reduces the likelihood of progressing from prediabetes to diabetes (typically, 6-10%/year) by half or more. But there is more to the story.

After successful treatment (pharmacotherapy or lifestyle), the majority of those who are prevented from progressing to frank diabetes still fulfill criteria for prediabetes (A1c 5.7-6.4). Between 20-50% of treated subjects are restored to currently recognized normal glucose levels.

The analysis by Perrault et al indicates that persons with prediabetes in whom normal glucose homeostasis was restored are half as likely to progress to frank diabetes over a 3-year, post-trial observation period as individuals whose glucose control was improved, but still reflected prediabetes. Striving for the best glucose control in prediabetes may have long-term benefits. ■

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Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■