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Evidence-Based Information for Hospitalists Intensivists, and Acute Care Physicians [ALERT]

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ABSTRACT & COMMENTARY

Noninvasive Ventilation Is More Effective Than Invasive Mechanical Ventilation for Acute Exacerbations of COPD but Remains Under-Utilized

By Kenneth P. Steinberg, MD, FACP

Professor, University of Washington School of Medicine, Seattle, WA, Editor of Hospital Medicine Alert

SYNOPSIS: Noninvasive ventilation has previously been shown to improve outcomes in studies of patients with acute respiratory failure secondary to an acute exacerbation of COPD. This study confirms the effectiveness of noninvasive ventilation in a large population-based registry and also demonstrates the wide variability of implementation and significant under-utilization of this therapy.

SOURCE: Tsai CL, et al. Comparative effectiveness of noninvasive ventilation vs invasive mechanical ventilation in chronic obstructive pulmonary disease patients with acute respiratory failure. *J Hospital Med* 2013; 8:165–172.

Noninvasive ventilation (NIV), referring to positive-pressure ventilatory support delivered via a nasal or full-face mask, has emerged as a useful treatment modality in patients with AECOPD and acute respiratory failure. Much of the literature suggests a mortality benefit with NIV compared with standard medical care in AECOPD. These data were collected in small-to-moderate sized research studies with many inclusion and exclusion criteria while only a few small, randomized controlled trials have directly compared NIV to invasive mechanical ventilation. The authors wished to better understand the adoption and effectiveness of NIV treatment for AECOPD in the "real-world" setting; their stated goals were (1) to characterize the use of NIV and invasive mechanical ventilation in AECOPD patients with acute respiratory failure; and (2) to compare the effectiveness of NIV vs invasive mechanical ventilation in daily practice.

The study was a retrospective cohort design using data from the 2006–2008 Nationwide Emergency

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Hospital Medicine [ALERT]

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Department Sample (NEDS), a component of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. The NEDS is nationally representative of all community hospital-based EDs in the United States. Patient visits were identified for this analysis if they carried any COPD-related diagnostic code as their primary or secondary ED diagnosis and any acute respiratory failure code as a primary or secondary diagnosis.

To compare the effectiveness of different ventilatory modes, patients were divided into 3 groups according to the ventilation mode they received: (1) NIV alone, (2) invasive mechanical ventilation alone, and (3) combined modes of NIV and invasive mechanical ventilation. Outcome measures were all-cause inpatient mortality, hospital LOS, hospital charges, and ventilator-related complications.

There were an estimated 101,000 visits annually for AECOPD with acute respiratory failure from approximately 4,700 US EDs. The mean patient age was 68 years. Ninety-six percent were admitted to the hospital. The mortality rate for those admitted was 9%, and the mean hospital LOS was 7 days. The use of invasive mechanical ventilation decreased from 28% in 2006 to 19% in 2008 (P<0.001), whereas NIV use increased slightly from 14% in 2006 to 16% in 2008 (P=0.049); the combined use of both ventilation modalities remained stable (approximately 4%). Inpatient mortality decreased from 10% in 2006 to 7% in 2008 (P<0.001).

The frequency of NIV use varied widely between hospitals, ranging from 0% to 100% with a median of 11%. In the cohort of AECOPD with acute respiratory failure, 43% received some form of ventilatory support: 36% received NIV, 56% received invasive mechanical ventilation, and 8% received combined use. Patients who received the combined use of NIV and invasive mechanical ventilation tended to have other comorbidities (congestive heart failure and pneumonia) compared with the NIV-alone or invasive mechanical ventilation-alone groups. NIV was used more often in hospitals with higher volumes of AECOPD and respiratory failure, in nonmetropolitan hospitals, and in hospitals in the Northeast.

In the propensity score-matched cohort, NIV use remained associated with significantly lower inpatient mortality (risk ratio: 0.54; 95% CI: 0.50-0.59, P<0.001), a shorter hospital LOS (mean difference, -3.2 days; 95% CI: -3.4 to -2.9 days, P<0.001), and lower hospital charges (mean difference, P<$35,012; 95% CI: -$36,848 to -$33,176, P<0.001), compared with invasive mechanical ventilation. Use of NIV was also associated with a lower rate of iatrogenic pneumothorax than invasive mechanical ventilation use (0.05% vs 0.5%, P<0.001).

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One of the strengths of this study is its use of a large national database that is representative of community hospital-based EDs across the United States. The study found that NIV use for acute respiratory failure from AECOPD, compared to invasive mechanical ventilation, was associated with a significant reduction of inpatient mortality, hospital LOS, hospital charges, and a modestly reduced risk of iatrogenic pneumothorax. As an analysis of an administrative database, and thus an observational study, the major limitations of the study include an inability to assume causality from the associations, and the possibility of unrecognized and unaccounted for confounding. Nevertheless, the findings are plausible based on the existing literature. That, plus the size of the database, makes the results more compelling.

There is some good news in this study: the use of NIV is rising, albeit modestly, and the use of invasive mechanical ventilation is decreasing. Mortality is also decreasing over time. But the disheartening news was that utilization of NIV remained very low (only 16% in 2008) and varied widely by patient and hospital characteristic. This is clearly an opportunity for improvement!

There are well-recognized contraindications to NIV, thus not every patient is a candidate for this treatment. Yet for good candidates, the use of NIV for acute respiratory failure secondary to AECOPD is not easy. Many systems-level barriers exist despite the demonstrated efficacy of NIV including lack of physician knowledge, insufficient respiratory therapist staffing and/or training, insufficient numbers of NIV machines in a given hospital, and the

amount of time available to safely and effectively set up NIV. It requires time and patience to fit a mask properly and adjust the settings so that the therapy is well tolerated. It is easier and faster to sedate and intubate a patient presenting with acute respiratory failure from AECOPD. Yet expediency, often a virtue, does not always lead to the best outcomes for this illness.

In summary, in this nationally representative database, NIV use is increasing for AECOPD with acute respiratory failure; however, its adoption remains low and varies widely between U.S. hospitals. NIV appears to be more effective and safer than invasive mechanical ventilation in the real-world setting. I believe that hospitalists can play an important role advocating for the increased use of NIV in their hospitals and promoting the use of NIV in patients with severe AECOPD. ■

ABSTRACT & COMMENTARY

Carbapenem-Resistant Enterobacteriaceae an Increasing Threat in the United States

By Stan Deresinski, MD, FACP, FIDSA

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This article originally appeared in the April 2013 issue of Infectious Disease Alert. *It was peer reviewed by Timothy Jenkins, MD. 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: The frequency of isolation of carbapenem-resistant Enterobacteriaceae is increasing in the U.S., with the highest prevalence in the northeastern region.

SOURCE: Centers for Disease Control and Prevention. Vital signs: carbapenem-resistant Enterobacteriaceae. *MMWR* 2013;62:165-70.

The emergence of resistance in Enterobacteriaceae to ertapenem, imipenem, meropenem, and doripenem due to the production of a carbapenemase is occurring in two primary enzyme groups. One group, also classified within Ambler Class B, is called metalo — lactamases because of a requirement for zinc for their catalytic activity. These metalloenzymes remain rare in the U.S., but are prevalent in a number of other countries — the New Delhi metallocarbapenemase (NDM) is a recently emerged example. Another group of carbapenemases, termed serine proteases because of the presence of this amino acid within their catalytic site, belong to Ambler Classes A, C, and D. One of these, KPC, first emerged in *Klebsiella pneunoniae* (hence the name, standing for *K. pneumoniae* carbapenemase), but has since spread via plasmids to other members of the Enterobacteriaceae. KPC-producing bacteria first emerged in the U.S. and are becoming increasingly prevalent both here and in other countries in which it has appeared.

■ COMMENTARY

The CDC has now assessed the extent of the problem of carbapenem-resistant Enterobacteriaceae (CRE) in the U.S. Among almost 4000 acute care hospitals that performed surveillance for either catheter-associated urinary tract infections or central line-associated blood stream infections during the first 6 months of 2012, 181 (4.6%) reported at least one CRE infection. This represented an approximate 4-fold increase in the last 10 years. CRE were reported by 3.9% of short-stay and 17.8% of long-term acute-care hospitals. The prevalence ranged from 3.2%-3.6% in the Midwest, South and West to 9.6% of hospitals in the Northeast. *Klebsiella* species were most frequently affected, followed by Enterobacter species and by *Escherichia coli*. In 2011, 4.2% of Enterobacteriaceae were carbapenem-resistant.

As pointed out in the CDC document, invasive infections, such as blood stream infection are associated with high mortality. Furthermore, CRE often contain multiple resistance mechanisms in addition to carbapenemases, making treatment of infections due to them highly problematic. They may rapidly spread within hospitals, where they are most prevalent.

The CDC has published extensive recommendations for control of CRE, including 8 core measures.[1] These are:

- Hand hygiene adherence with monitoring and feedback
- Contact precautions
- Healthcare personnel education
- Minimization of device (e.g., vascular access devices, endotracheal tubes, urinary catheters) utilization
- Patient and staff cohorting
- Procedures for rapid notification of appropriate personnel by the laboratory
- Antimicrobial stewardship
- Screening for CRE colonization

For hospitals that rarely or have never previously identified a CRE[2], they recommend contact

isolation in a single room, reinforcement of hand hygiene, and education of staff about prevention measures. They further recommend screening of epidemiologically-linked patient contacts with, at a minimum, stool, rectal or perirectal cultures. Consideration may be given to a point-prevalence study of the affected unit, as well as to preemptive contact precautions. If additional colonizations/infections are detected, consideration may be given to cohorting patients and staff. ■

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2. CDC. 2012 CRE Toolkit- Guidance for Control of Carbapenem-Resistant Enterobacteriaceae (CRE). Appendix B: General Approach to Carbapenem-resistant Enterobacteriaceae (CRE) Control in Facilities that Rarely or Have Not Identified CRE. http://www.cdc.gov/hai/organisms/cre/cre-toolkit/rCREprevention-AppendixB.html

ABSTRACT & COMMENTARY

Lowering Blood Pressure but Raising the Risk of Hip Fracture

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips serves on the speakers bureau for PotomaCME.

This article originally appeared in the March 15, 2013, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Senior Attending Physician, Long Island Jewish Medical Center, NS/LIJ Health Care System, New Hyde Park, NY. Dr. Brunton serves on the advisory board for Abbott, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

SYNOPSIS: The risk of hip fracture goes up for about 6 weeks immediately after older people start taking antihypertensives.

SOURCE: Butt DA, et al. The risk of hip fracture after initiating antihypertensive drugs in the elderly. *Arch Intern Med* 2012; 172:1739-1744.

Taking antihypertensive drugs is known to be associated with increased risk of falling and hip fracture in older people, but most of what is known about this is based on studies done in people who are taking these medications chronically. These authors set out to learn about the risk of falls and hip fractures immediately after initiation of antihypertensive drugs in community-dwelling people.

To do this, they identified all Ontario residents aged 66 years and older who got a first prescription for a thiazide diuretic, angiotensin II converting-enzyme (ACE) inhibitors, angiotensin II receptor antagonist/blockers (ARBs), a calcium channel blocker, or a beta-adrenergic blocker. They linked these patients to the national physician claims database, which provides detailed diagnostic and procedural information. Because of the richness of these data, they were able to exclude patients who were prescribed these agents for something other than hypertension (for example, cardiomyopathy or essential tremor). They also excluded those who were previously prescribed these drugs at any point in the preceding year, those with pathologic fractures, and those who were institutionalized. The main outcome was first occurrence of a hip fracture. They compared incidence of hip fracture in the first 45 days after a new antihypertensive prescription with two 45-day periods in the year before they started the treatment.

The cohort had a mean age of 81 years and was mostly women (about 81%). ACE inhibitors were the most commonly prescribed agents (30%), with ARBs being the least-commonly used (5%). There were 301,591 newly treated hypertensive elderly patients who had 1463 hip fractures during the 10-year period of data collection.

People who started an antihypertensive drug for the treatment of hypertension had a 43% increased risk of hip fracture during the first 45 days of treatment. The risks were generally consistent among the five different classes of antihypertensive drugs, but only the ACE inhibitors and beta-blockers were statistically significantly associated with increased risk as a class. Comparing risk of hip fractures for the first 2 weeks to the next 4 weeks after starting the drug showed that the hip fracture risk after starting any antihypertensive drug for the treatment of hypertension was actually highest (54%) for weeks 3-6. This increased trend was not seen with thiazide diuretics and was most pronounced for ACE inhibitors. Statistically controlling for various confounders, including psychotropic medications, did not affect these relationships.

■ COMMENTARY

What is new here is the finding that the risk of hip fracture increases immediately after starting a new antihypertensive agent in older people, particularly for ACE inhibitors and beta-blockers. The authors discuss several different mechanisms, including orthostatic hypotension, confusion, venous pooling, and extracellular volume decreases, depending on the agent.

In their discussion, the authors note that treating hypertension reduces the risk of cardiovascular disease in the long run but increases the risk of fall-related injuries in the short run. They note that such falls cause functional, cognitive, and physical effects similar to those that result from myocardial infarction and stroke.[1,2] In fact, they point out that the incidence of nonfatal cardiovascular events in hypertensive elderly patients and serious fall injuries in the elderly at risk of falls is essentially the same, at 16%.[2,3] All of a sudden, the decision of when and how to treat hypertension in the elderly is not as simple as it was. At the very least, we need to advise our older patients that they will be slightly more likely to break a hip in the first 6 weeks after starting a new drug for hypertension. ■

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Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital

This article originally appeared in the April 2013 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. Fink is a retained consultant for MAQUET and Dr. Beal reports no financial relationships relevant to this field of study.*

SYNOPSIS: Mediterranean diet can reduce risk for stroke

SOURCE: Estruch R, et al, for the PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; Feb. 25. DOI: 10.1056/NEJMoa1200303. [Epub ahead of print].

The PREDIMED investigators from Barcelona, Spain, reported the results of their multicenter, randomized dietary treatment trial of the effects of three different diets on cardiovascular events — a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet that included advice to reduce dietary fat. The Mediterranean diet is characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation consumed with meals. A number of observational cohort studies suggested that this diet, over many years, might confer a reduced risk of cardiovascular disease, but this was the first large-scale, randomized study that directly compared diets. The primary endpoint was the rate of major cardiovascular diseases (myocardial infarction, stroke, death from cardiovascular causes), and the trial was stopped early (median follow-up of 4.8 years) when an interim analysis showed a significant difference in outcomes, based on which diet was instituted.

The enrolled subjects were free of cardiovascular disease, but had risk factors for disease — type 2 diabetes mellitus, or at least three of the following other risk factors: smoking, hypertension, elevated LDL, low HDL, obesity, or family history of premature coronary heart disease. A total of 7447 patients were enrolled (ages 55 to 80 years); 57% were women, and they were followed for a mean time of 4.8 years before the study was terminated. In a multivariable-adjusted analysis, the hazard ratios were 0.70 (95% confidence interval [CI], 0.54-0.92) for the Mediterranean diet with extra virgin olive oil, and 0.72 (95% CI, 0.54-0.96) for the group assigned to the Mediterranean diet with nuts, vs the control group. For stroke alone, the hazard ratios for the two Mediterranean diets were 0.67 (olive oil) and 0.54 (nuts). Adherence to the Mediterranean diet results in a clinically and statistically significant reduction in cardiovascular events, especially stroke. ■

ABSTRACT & COMMENTARY

Left Atrial Appendage Occlusion vs Warfarin for Nonvalvular AF

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

SOURCES: Reddy VY, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial. *Circulation* 2013;127:720-729. Alli O, et al. Quality of life assessment in the randomized PROTECT AF trial of patients at risk for stroke with non-valvular atrial fibrillation. *J Am Coll Cardiol* 2013; Feb. 28. [Epub ahead of print.]

Atrial fibrillation (AF) is a major source of morbidity in patients and cost to the health care community. In the presence of risk factors for thromboembolism, AF is associated with an increased risk of stroke, and this risk is reduced with warfarin. However, warfarin has limitations, including the risk of bleeding and the need for regular blood tests. The left atrial appendage (LAA) is thought to be a nidus for thrombus that can result in stroke or systemic embolism. The Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) trial was a randomized controlled trial of percutaneous device closure of the LAA with the Watchman device vs continued warfarin therapy. In these studies, Reddy and colleagues present the final long-term outcomes of this trial, and Alli et al present the quality-of-life (QOL) outcomes.

The main inclusion criteria for the PROTECT AF study were age > 18 years; a history of paroxysmal, persistent, or permanent nonvalvular AF plus at least one additional stroke risk factor (age ≥ 75 years, hypertension, diabetes mellitus, heart failure, prior stroke, transient cerebral ischemic attack, or systemic thromboembolism); and eligibility for warfarin therapy, i.e., a CHADS2 score ≥ 1. Exclusion criteria were the presence of atrial septal defect, mechanical prosthetic heart valve, patent foramen ovale accompanied by atrial septal aneurysm (because of the potential for paradoxical embolization), left ventricular ejection fraction < 30%, intracardiac thrombus, morphologically complex (mobile or ulcerated) aortic atheroma, or symptomatic carotid artery disease. Patients (n = 707) were randomized in a 2:1 fashion to receive the device or continue warfarin. The initial results have been presented, but in these studies we are given the longer-term efficacy and safety outcomes, and the QOL outcomes.

For patients randomized to Watchman device implantation (n = 463), warfarin was continued for ≈ 45 days, followed by clopidogrel for 4.5 months and then lifelong aspirin. In the warfarin group (n = 244), the time in therapeutic range was 66%. In the study by Reddy et al, after 2.3 ± 1.1 years of follow-up (1588 patient years), the event rates of the composite primary efficacy endpoint of stroke, systemic embolism, and cardiovascular death were 3.0% and 4.3% (percent per 100 patient years) in the Watchman and warfarin groups, respectively (relative risk [RR], 0.71; 95% confidence interval [CI], 0.44-1.30% per year), which met the criteria for non-inferiority. There were more primary safety events in the Watchman group (5.5% per year; 95% CI, 4.2-7.1% per year) than in the control group (3.6% per year, 95% CI, 2.2-5.3% per year; RR, 1.53; 95% CI, 0.95-2.70% per year). When the effect of LAA closure was isolated from complications of implantation and concomitant transient anticoagulation in a secondary analysis, the Watchman device was superior to warfarin (probability of superiority = 0.953). Among patients with stroke before they entered the study, the two strategies were equally effective, with rates of 5.3% per year and 8.2% per year, respectively, (RR, 0.64; 95% CI, 0.24-1.74% per year). Similar trends were seen in patients with CHADS2 scores ≥ 2. The authors conclude that the "local" strategy of LAA closure is noninferior to "systemic" anticoagulation with warfarin, and that PROTECT AF has, for the first time, implicated the LAA in the pathogenesis of stroke in AF.

In the study by Alli et al, QOL using the SF-12-V2 measurement tool was obtained at baseline and 12 months in a subset of 547 patients (361 device and 186 warfarin patients). The analysis cohort consisted

of those for whom either paired QOL data were available after 12 months of follow-up or in patients who died. In the device and warfarin arms respectively, the total physical score improved in 34.9% and 24.7%, and was unchanged in 29.9% and 31.7% ($P = 0.01$). There was a significant improvement in QOL in patients randomized to device for total physical score, physical function, and in physical role limitation compared to controls. Interestingly, there were significant differences in the change in total physical score among warfarin-naïve and not-warfarin-naïve subgroups in the device group compared to controls, but larger gains were seen with the warfarin-naïve subgroup with a 12-month change of 1.3 ± 8.8 vs -3.6 ± 6.7 ($P = 0.0004$) device compared to warfarin. The authors conclude that patients with nonvalvular AF at risk for stroke treated with LAA closure have favorable QOL changes at 12 months vs patients treated with warfarin.

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The results of these studies are very provocative, suggesting that for patients with any type of nonvalvular AF (paroxysmal, persistent, or permanent), closure of the LAA can result in similar outcomes to warfarin with improved QOL. Based on these results, the device has been approved in Europe and now carries a class IIB recommendation in the European guidelines. However, it should be emphasized that this device is not FDA approved for use in the United States.

The PROTECT AF trial is a well-designed study with large numbers of patients for a device trial (although small numbers for a drug trial). The consistency of the results across subgroups and across intention-to-treat and per-protocol analyses, as well as in the landmark analysis (after the brief period of warfarin in the device group), strengthen the conclusions drawn by the authors. However, several issues should be noted. First, patients with significant aortic and carotid atheroma were excluded, as were patients who cannot tolerate warfarin. The role of LAA occlusion in these patient groups remains to be studied. Second, the follow-up period was really only medium-term (2.3 years) and long-term data will be necessary to definitely make conclusions between groups. Third, the cost effectiveness of this strategy has yet to be presented in the U.S. system. Some patients may prefer a single procedure to avoid long-term warfarin, and the QOL data suggest this is a reasonable strategy. But what costs this will impose and who will pay remain to be determined. Overall, however, these data are encouraging that we may one day be able to offer our patients a "local" strategy to reduce the risk of stroke as an alternative to systemic anti-coagulation, and they may feel better for it. ■

ABSTRACT & COMMENTARY

Tight vs Loose Rate Control in Permanent Atrial Fibrillation

By John P. DiMarco, MD, PhD

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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

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

SOURCE: Gomes T, et al. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ* 2013; 185:E121-E127.

The Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) trial compared strict rate control vs lenient rate control in patients with permanent atrial fibrillation. In this substudy, the RACE II investigators report results based on three groups of patients: those with successful strict rate control, those with unsuccessful rate control, and those with lenient rate control. In RACE II, lenient rate control was defined as a resting heart rate < 110 beats per minute (bpm). Strict rate control required a resting heart rate < 80 bpm and a heart rate < 110 bpm during moderate exercise. The primary outcome was a composite of cardiovascular morbidity and mortality. Patients in the strict rate control group were classified as failures if one of the heart rate criteria was not met. Heart rate control was assessed at the end of a dose-adjustment phase. Quality of life was assessed with several instruments, including the Medical Outcome Study SF-36, the University of Toronto AF Severity Scale, and the

Multidimensional Fatigue Inventory 20.

There were 608 patients included in this analysis. In the strict rate control group, 203 patients achieved strict rate control and 98 patients did not meet target heart rate. The reasons for failure of strict rate control included manifest drug-related adverse effects, no or acceptable symptoms despite faster heart rates, and an inability to achieve rate control with drug therapy. Among the patients in the lenient rate control group, 69% were controlled with a single AV nodal blocking agent or did not require any drug therapy for rate control. Only 31% required two or more AV nodal blocking agents. In contrast, in the strict rate control group, 72% of patients required two or more agents. There was no difference in the primary outcome after the dose-adjustment phase with 27 of 203 (13.3%) in the successful strict control group, 14 of 98 (14.3%) in the failed strict control group, and 35 of 307 (11.4%) in the lenient group reaching a primary endpoint. There also were no differences between the three groups in all-cause mortality or when patients with an ejection below 40% were analyzed separately. During follow-up, additional visits were more frequently required in the strict rate control group. There were no significant changes in mean ejection fractions in any of the three groups over time. There was also no change in any of the reported symptom scales or in quality of life between the three groups. The authors conclude that lenient rate control is as effective as strict rate control even if patients who fail to achieve strict rate control are excluded.

■ COMMENTARY

RACE II data have now shown that very intense heart rate control in patients with atrial fibrillation is not required for reasonable short-term outcomes. However, physicians should still be cautious in accepting heart rates in the upper portion of the acceptable range. Most of the patients in the RACE II lenient control group had resting rates below 100 bpm, so we would expect them to do reasonably well. We must also remember that tachycardia-associated cardiomyopathies at slower heart rates (110-130 bpm) may take years to develop and RACE II was a relatively short-term study. I continue to try to keep the resting heart rate in a range I know to be safe (70-90 bpm) and will reevaluate patients outside this range or with symptoms at more frequent intervals. ■

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CME QUESTIONS

1. Compared to invasive mechanical ventilation, noninvasive ventilation for acute exacerbations of COPD has been shown be associated with:

a. Lower rate of iatrogenic pneumothorax.
b. Decreased inpatient mortality.
c. Shorter hospital length of stay.
d. All of the above.

2. A percutaneously delivered left atrial appendage occlusion device for preventing systemic thromboemboli in patients with atrial fibrillation has been shown to be:

a. Superior to warfarin.
b. Non-inferior to warfarin.
c. Inferior to warfarin.
d. Technically unsafe.

3. Antihypertensives are associated with an increased risk of hip fractures in older people:

a. Only for the first 2 weeks after initiation.
b. Only after long-term (> 6 months) use.
c. For thiazide diuretics only.
d. That is similar to the incidence of nonfatal cardiovascular events in hypertensive elderly patients.

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.

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Extended Treatment of VTE with Dabigatran vs Warfarin

Source: Schulman S, et al. *N Engl J Med* 2013;368:709-718.

Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a "traditional" course of warfarin. ■

Selection Criteria for Lung Cancer Screening

Source: Tammemagi M, et al. *N Engl J Med* 2013;368:728-736.

The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer. ■

Special Subgroups in Hypertension: Obese Hypertensives

Source: Weber MA, et al. *Lancet* 2013; 381:537-545.

The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with *existing* CV disease), subjects with *normal* body weight bear a disproportionately *greater* risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most

frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination. ■

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

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Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. *Lancet* 2013; 381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. *JAMA* 2013;309: 578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

PHARMACOLOGY WATCH

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

New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, 2 × 2 factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (*JAMA* 2013;309:1241-1250). Editorialists in the same issue of *JAMA* immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The *JAMA* editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that "these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease." (*JAMA* 2013;309:1291-1292.) Another editorialist, however, suggests that "limitations in the design and execution" of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of "softer" endpoints such as coronary revascularization and hospitalization for angina.

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Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, "including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy." (*JAMA* 2013;309:1293-1294.) ■

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (*BMJ* 2013;346:f880). ■

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥ 66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (*Ann Intern Med* 2013;158:447-455). ■

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in *The New England Journal of Medicine* last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug's effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget's disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee's recommendations. ■