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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

PCI Outcomes in Women vs Men

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

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

SOURCE: Anderson ML, et al. Short- and long-term outcomes of coronary stenting in women versus men: Results from the national cardiovascular data registry Centers for Medicare & Medicaid services cohort. *Circulation* 2012;126:2190-2199.

Percutaneous coronary intervention (PCI) is performed in more than 600,000 patients annually in the United States, and women make up approximately one-third of this population. There are conflicting data on the outcomes of PCI in women vs men, and there are few gender-specific data in the contemporary PCI era.

Anderson and colleagues linked the National Cardiovascular Data Registry (NCDR) with Medicare's database and studied 426,996 patients ≥ 65 years of age undergoing PCI between 2004 and 2008, including 180,752 women. Median follow-up was 20 months. There were significant baseline differences between the women and men, as expected. Women were older (75.8 vs 74.1 years) and were more likely to have diabetes, congestive heart failure, and hypertension. Men were more likely to have dyslipidemia, prior myocardial infarction (MI), and prior coronary artery bypass grafting. Women were more likely to have acute coronary syndromes (65.1% vs 61.5%) and less likely to have stable angina (14.9% vs 16.5%) as the indication for PCI.

Procedural success rates were similar between genders (96.3% vs 96.2%); however, women experienced more in-hospital complications than men: mortality 2.2% vs 1.6%, peri-procedural MI 1.3% vs 1.2%, bleeding 4.4% vs 2.3%, and vascular complications 1.3% vs 0.7%. Women had higher rates of in-hospital stroke (odds ratio [OR] 1.50), renal failure (OR 1.25), cardiogenic

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[INSIDE]

Clinical Cardiology [ALERT]

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shock (OR 1.59), and incident heart failure (OR 1.59).

Long-term outcomes were statistically adjusted for > 50 variables. Although women had higher unadjusted long-term mortality, after adjustment women had a lower hazard ratio [HR] for death (0.92, 95% confidence interval [CI], 0.9-0.94). There were no differences between men and women in the rates of MI (HR 0.99; 95% CI, 0.95-1.03), bleeding (HR 0.99; 95% CI, 0.98-1.09), or repeat revascularization (HR 0.99; 95% CI, 0.97-1.02). The authors also compared outcomes based on whether bare-metal stents (BMS) or drug-eluting stents (DES) were used. After multivariable adjustment, the risk of death was lower with DES use than with BMS use in both women and men (women: HR 0.78; 95% CI, 0.76-0.81; men: HR 0.77; 95% CI, 0.74-0.79), as were the risks of MI and repeat revascularization (women: HR 0.93; 95% CI, 0.90-0.97; men: HR 0.91; 95% CI, 0.88-0.94). The authors conclude that in contemporary coronary stenting, women have a slightly higher procedural risk than men but have better long-term survival. In both sexes, use of a DES is associated with lower long-term likelihood for death, MI, and revascularization.

■ COMMENTARY

This is very helpful in clinical practice and is important for several reasons. First, women historically made up a small proportion of the pivotal randomized, controlled trials that led to approval of stents. This is a very large study with a high proportion of women. Second, this study reflects the use of contemporary PCI techniques, including a large number of patients receiving DES (albeit likely first-generation DES in most). Third, the statistical techniques were robust. These factors lend weight to the conclusions drawn from these data. However, several important limiting factors should be acknowledged in interpreting this dataset. First, it is an observational study, not a prospective randomized study, and there were baseline differences between groups. Although the authors tried to address this by adjusting for more than 50 covariates, there may still be unmeasured confounders that could influence the data. Second, the authors were only able to link the NCDR and Medicare databases in 68% of cases, which may also bias the results. Third, the authors were not able to ascertain provider-specific outcomes or procedural volumes, which may affect outcomes, but the effects of such individual statistics are likely to be diluted over the more than 900 institutions reporting to the databases.

The reasons for the paradoxical early worse outcomes but better long-term outcomes in women remain unknown. The authors suggest there may be differences in pre-procedural care, such as delayed diagnosis due to atypical symptoms, that may influence early outcomes. This would be consistent with prior observational studies, but cannot be ascertained from the current dataset. Most prior studies have shown higher peri-procedural bleeding outcomes in women, which can certainly influence outcomes. This study confirmed a higher in-hospital bleeding rate in women, even after multivariable adjustment. In addition, there was a higher vascular complication rate, driven by a higher rate of pseudoaneurysms in women. The rate of radial vs femoral access, and the use of vascular closure devices are not mentioned, and these may influence the rate of pseudoaneurysm formation. Why do women fare better in the long-term? The authors suggest that perhaps after the initial diagnosis of coronary artery disease, women may receive more aggressive secondary prevention measures and more rapid attention to recurrent symptoms. Whether other factors are at play as well remains to be tested. The results of this study set the scene for further mechanistic studies into the relative benefits of medical therapy and PCI based on gender. ■

ABSTRACT & COMMENTARY

CABG Better in Elderly, PCI Better in Young?

By Andrew J. Boyle, MBBS, PhD

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SOURCE: Flather M, et al. The effect of age on outcomes of coronary artery bypass surgery compared with balloon angioplasty or bare-metal stent implantation among patients with multivessel coronary disease. A collaborative analysis of individual patient data from 10 randomized trials. *J Am Coll Cardiol* 2012;60:2150-2157.

As our population ages and outcomes from revascularization also improve, more elderly patients are being referred for coronary artery bypass graft surgery (CABG) and for percutaneous coronary intervention (PCI). Current guidelines do not include age-specific recommendations for the choice of revascularization technique. Although there are several clinical trials comparing CABG and PCI, the effects of age on the outcomes remain uncertain. Therefore, Flather and colleagues performed a meta-analysis using data from 10 randomized controlled trials that compared CABG with PCI to ascertain the effects of age on outcomes from these procedures. Notably, all of the studies included only used balloon angioplasty or bare-metal stents; none of these studies used drug-eluting stents. The authors used individual patient-level data from 7812 patients and divided them into tertiles of age (≤ 56.2 years, 56.3-65.1 years, and ≥ 65.2 years). The primary outcome was all-cause mortality. Secondary outcomes were the composite of death or myocardial infarction (MI), repeat coronary revascularization, and angina at 1 year of follow-up.

There were significant baseline differences between the age groups, as expected. Older patients were more likely to be female and to have diabetes, hypertension, peripheral vascular disease, heart failure, and triple vessel disease, but were less likely to be smokers or to have a history of MI (all $P < 0.001$). However, within each age tertile, the baseline characteristics were well matched between those randomized to CABG or PCI.

Younger patients randomized to PCI had lower mortality than CABG (8% vs 11%), whereas older patients randomized to PCI had higher mortality than CABG (24% vs 20%). The CABG-to-PCI adjusted hazard ratio [HR] for all-cause mortality was described for each tertile of age, with values greater than 1.0 signifying that CABG was associated with a higher mortality than PCI, whereas values lower than 1.0 indicated CABG had lower mortality. The HR was 1.23 in the young (95% CI, 0.95-1.59), 0.89 in the middle tertile (95% CI, 0.73-1.10), and 0.79 in the oldest tertile of age (95% CI, 0.67-0.94). This relationship was the same for the combined secondary endpoint of death or MI. Of note, the CABG-to-PCI HR for mortality decreased with age and crossed 1.0 at age 59 years, suggesting that CABG is associated with lower mortality than PCI in patients > 59 years of age, but PCI is associated with lower mortality in patients < 59 years of age. The relationship between age and outcomes was similar when stratified by diabetes. The CABG-to-PCI HR for mortality was < 1.0 (i.e., favored CABG) among patients > 63 years without diabetes and among patients > 47 years with diabetes. In all age groups, PCI was associated with a higher rate of repeat revascularization than CABG. The rate of stroke was only available in six studies, but increased significantly with age and assignment to CABG. The authors conclude that patient age modifies the comparative effectiveness of CABG and PCI on hard cardiac events, with CABG favored at older ages and PCI favored at younger ages.

■ COMMENTARY

The debate continues about which revascularization strategy, CABG or PCI, is best. The recently presented FREEDOM trial suggests that diabetics fare better with CABG than PCI. The SYNTAX trial suggested that those with more anatomically complex coronary disease have better outcomes with CABG. The current study suggests that aging may also play a role in selecting the most appropriate subsets of patients for a particular treatment. It should be noted that this is an observational study and not a randomized trial, and as such there may be selection bias for either treatment that cannot be fully accounted for by statistical adjustment.

It may be somewhat counterintuitive that older patients have better outcomes with CABG and younger patients have lower mortality with PCI.

CABG has traditionally been thought of as a superior long-term treatment option. Therefore, one would expect that younger patients have longer to live and longer to gain the benefits of CABG. One explanation may be that age acts as a surrogate for more extensive coronary artery disease. Although the authors corrected for the presence of triple vessel disease, they were unable to get further detail of anatomical extent of atherosclerosis, such as the SYNTAX score. Outcomes with PCI or CABG are worse with extensive, complex coronary disease and this may be influencing the results with age presented in this paper.

These results will not change guidelines, as they are observational in nature. However, they may help clinicians steer toward a particular strategy if clinical equipoise exists in parameters other than age. Further prospective studies are needed to elucidate the effects of aging on PCI and CABG outcomes, particularly in the era of drug-eluting stents, and taking into account parameters other than death and MI, such as cost-effectiveness and quality-of-life measures. ■

ABSTRACT & COMMENTARY

Risk of Angioedema with Drug Therapy

By Michael H. Crawford, MD, Editor

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

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

■ COMMENTARY

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

ABSTRACT & COMMENTARY

Risk of Bleeding with Warfarin Therapy for 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.

SOURCE: Gomes T, et al. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ* 2012; Nov. 26. [Epub ahead of print.]

This paper details the result of a population-based cohort study of all Ontario, Canada, residents older than 66 years of age who began warfarin therapy for atrial fibrillation over an 11-year period. Patients were identified by the authors from data in the Ontario Health Insurance Plan. Patients were included if they had a hospital or office visit diagnosis of atrial fibrillation and began warfarin during this time period. Medical records were then surveyed for the occurrence of major hemorrhages. This was defined as a visit to an emergency department or admission to a hospital for hemorrhage during warfarin therapy. Patients were followed for up to 5 years after starting warfarin. Hemorrhage was classified by anatomic site using standard definitions. If patients had more than one admission for hemorrhage, only the first event was included.

During the 13-year study period, there were 125,195 patients who began therapy with warfarin in the setting of a diagnosis of atrial fibrillation. This was 47% of all new users of warfarin in this age group during this time period. Of these patients, 69% had an estimated CHADS2 score ≥ 2. In this inception cohort, the cumulative incidence of hemorrhage was 1.0% at 30 days, 4.1% at 1 year, and 8.7% at 5 years. During the study, the overall risk of hemorrhage was 3.8% per patient year. The annualized risk was highest during the first 30 days of therapy (11.8%) and 3.4% during the follow-up period. Hemorrhage was more common as the CHADS2 score increased. Patients with a CHADS2 score ≥ 4 had a 16.7% hemorrhage rate per person year in the first 30 days and 6.0% per year afterwards. By contrast, those with CHADS2 scores < 2 had hemorrhage rates of 1.8% per person year with a score of 0 and 2.5% per person year with a score of 1. Hemorrhage rates were higher among patients older than 75 years (4.6% in older patients vs 2.9% in younger patients). Upper and lower gastrointestinal hemorrhage accounted for 63% of the hemorrhage-related hospitalizations, intracranial hemorrhage for 5%, and other sites, mostly genitourinary, for 39%. There were 1963 deaths due to hemorrhage in the hospital or within 7 days after discharge. Intracranial hemorrhage had the highest mortality (41.7%) compared to gastrointestinal hemorrhage (14.7%) and other sites of hemorrhage (12.6%).

The authors conclude that in a large inception cohort of patients with atrial fibrillation, hemorrhage is common during both the first 30 days and subsequent months of warfarin therapy and is related to risk factors in the CHADS2 score and also to age. The risk of hemorrhage is higher than has been seen in recent published randomized trials of anticoagulation therapy. The mortality rate associated with hemorrhage, particularly intracranial hemorrhage, is extremely high.

■ COMMENTARY

Since the new oral anticoagulants, dabigatran and rivaroxaban, were approved for stroke prevention in patients with atrial fibrillation, concerns have been raised about bleeding problems with these agents that had not been prominent in the randomized clinical trials. Reports in both the medical literature and the lay press have complained that the level of anticoagulation cannot be monitored with standard tests and that there is no available rapid antidote. Although these statements about the new oral anticoagulants are true, this paper points out that bleeding with warfarin is also a major concern. Particularly striking are the very high rates of bleeding with warfarin during the first month of therapy and the shockingly high mortality rates seen during hospitalizations for hemorrhage. We have scoring systems for both stroke risk and bleeding risk in patients on anticoagulant therapy. The data in this paper indicate that applying these risk scores in clinical practice is still problematic. ■

ABSTRACT & COMMENTARY

Preventing Inappropriate ICD Shocks

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

SOURCE: Moss AJ, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;367:2275-2283.

This study, the Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy (MADIT-RIT), was designed to test the hypothesis that programming implantable cardioverter-defibrillator (ICD) therapies with higher detection rates or delayed detection before initiation of therapy would decrease inappropriate shocks in ICD patients. The study enrolled 1500 patients at 98 ICD implanting centers. Patients could have any form of ischemic heart disease, had to be in sinus rhythm at the time of enrollment, and met approved criteria for implantation of an ICD or CRT-D device for primary prevention of sudden death. Patients were randomized to three types of programming. The conventional therapy group received a device programmed with two detection zones: 1) a ventricular tachycardia zone for heart rate between 170-199 beats per minute with a 2.5-second delay and atrial discriminators, and 2) a second zone beginning at 200 beats per minute for faster VT or VF with a 1-second delay before delivery of therapy, either antitachycardia pacing (ATP) or shock. Group two patients received a device programmed with a monitor only zone between 170-199 beats per minute with a therapy prescribed at 200 beats per minute after a 2.5-second delay. Patients in the delayed therapy group received a device programmed to three detection zones: one at 170-199 beats per minute with rhythm detectors on and a 60-second delay before initiation of therapy, a second VT detection zone beginning at 200 beats per minute with rhythm detection on and a 12-second delay before therapy, and a third zone at 250 beats per minute with a 2.5-second delay before initiation of therapy. The devices used in this trial were commercially available from Boston Scientific. The decision for dual-chamber ICD vs a CRT-D device was at the discretion of the investigator. The primary endpoint was the first occurrence of inappropriate therapy, including both ATP or shock. All therapy electrograms were reviewed by a core laboratory and classified as appropriate or inappropriate by a three-member committee. The secondary endpoints were death from any cause and first episode of syncope.

The clinical characteristics of the 1500 patients enrolled were similar to those for all patients receiving primary prevention ICDs in the United States, except for a younger mean age. Patients with both ischemic and non-ischemic heart disease were included in equal proportions. Approximately equal numbers of patients received dual-chamber ICDs and CRT-D devices. As compared with the conventional therapy group, the high rate and delayed therapy groups were less likely to receive both appropriate therapy and inappropriate therapy during a follow-up duration of 1.4 years. In the conventional therapy group, 22% received appropriate therapy and 20% received inappropriate therapy. In the high-rate therapy group, 9% of patients received appropriate therapy and 4% received inappropriate therapy. In the delayed therapy group, 6% of patients received appropriate therapy and 5% received inappropriate therapy. This reduction in therapy was due to much less utilization of antitachycardia pacing. When the total occurrences of therapy were examined, application of antitachycardia pacing in the high-rate therapy and delayed therapy group was reduced by more than 75% compared to the conventional therapy group. Life-table estimates of the time to first occurrence of inappropriate therapy showed that the conventional therapy group had a 29% probability of inappropriate therapy at 2.5 years while the inappropriate therapy rate at that time point was only 6% in both the high-rate and delayed therapy groups. Mortality was also reduced in both the high-rate therapy and delayed therapy groups. There were 34 deaths in the conventional therapy group, compared to 16 deaths in the high-rate group and 21 deaths in the delayed therapy group. The incidence of syncope was similar in the three groups.

The authors conclude that ICD programming to less aggressive detection settings reduces inappropriate and unnecessary therapies and may have beneficial effects on mortality.

■ COMMENTARY

It's not a real surprise that less aggressive detection zones will reduce therapy delivery in primary

prevention ICD recipients, but MADIT-RIT provides the most definitive data supporting this conclusion. What is an important finding is that there appears to be additional benefits in terms of overall mortality with almost no downside. We're not told if there were any episodes of slow sustained VT without syncope that fell below the programmed detection criteria, but this should be an unusual occurrence in a primary prevention population. The incidence of syncope was the same in all three groups, pointing out that not all syncope in low ejection fraction cardiac patients is due to VT.

Most ICDs in the United States are placed for primary prevention, but the default settings are more appropriate for patients with a history of sustained monomorphic VT. Although wavelet morphology and atrial discrimination algorithms may be helpful, MADIT-RIT shows that they are often inadequate tools for preventing clinically unnecessary shocks. Manufacturers should consider changing the default settings while still allowing electrophysiologists to modify the programming when needed. ■

ABSTRACT & COMMENTARY

Current Drug Usage in Atrial Fibrillation

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

SOURCE: Piccini J, et al. Pharmacotherapy in Medicare beneficiaries with atrial fibrillation. *Heart Rhythm* 2012;9:1403-1408.

This paper reviews drug therapy in patients with atrial fibrillation in the Medicare population. The author extracted a 5% sample of Medicare beneficiaries who were enrolled in Medicare Part D. They identified patients with prevalent atrial fibrillation as of January 1, 2006, and as of January 1, 2007. Prevalent atrial fibrillation was defined as the presence of an atrial fibrillation diagnosis on an inpatient claim or more than two outpatient claims during the previous calendar year. Part D pharmacy prescriptions that were filled during the first 4 months of each of the 2 years were then analyzed. Comorbid conditions were determined from the Medicare claims files. The rates of drug usage were then adjusted for age and gender so that the values could be compared to other databases.

There were 27,174 Medicare patients with prevalent atrial fibrillation enrolled in Medicare Part D in 2006. Enrollment nearly doubled to 45,711 in 2007. Among patients with prevalent atrial fibrillation in the 2007 cohort, 74% were on rate control medications, with beta-blockers (52.8%) being the agents more commonly used. Digoxin was used by 30% and calcium channel blockers (dltiazem or verapamil) by 19%.

Membrane active antiarrhythmic agents were used in 19.1% of the 2007 cohort. Class Ia agents were used in less than 1%, Class Ic agents in 3.9%, and Class III agents in 14.9%. Of the Class III agents, amiodarone was prescribed more frequently (9.4%) than dofetilide (0.5%) and sotalol (5.1%). Warfarin anticoagulation was used in 59% of the patients and antiplatelet agents in 9.1%. There were minor differences in drug therapy depending on the presence of heart failure. Class Ia drug therapy was less common and amiodarone use was more common if heart failure was present. Oral anticoagulation was comparable between groups with and without heart failure. Interestingly, anticoagulation therapy decreased with increasing CHADS2 scores. Warfarin was used in 62% of the patients with a CHADS2 score of 0 and 1, but only 55%, 52%, and 49% of patients with CHADS2 scores of 4, 5, and 6.

The authors conclude that medication use in atrial fibrillation varies according to underlying risks and comorbid diseases. In older patients, rate control strategies are more common than rhythm control strategies. There is an inverse relationship between CHADS2 risk score for stroke and the use of oral anticoagulants.

■ COMMENTARY

This survey covers Medicare patients treated in 2006 and 2007. Since these data were collected, dronedarone, a non-iodinated compound similar to amiodarone, was released with some enthusiasm. Unfortunately, subsequent data have raised questions about both the safety and efficacy of dronedarone, and it's likely that the medication profile reported here is still largely accurate.

The profile shows how disappointing antiarrhythmic therapy for atrial fibrillation remains. Most Medicare patients are treated with a rate-control strategy and when a rhythm-control strategy is followed, amiodarone, an agent with significant toxicity, is the drug most commonly used.

There have been no recent major advances in drug therapy for atrial fibrillation. It remains to be shown that catheter ablation can become effective enough long-term and available enough to the millions of patients with atrial fibrillation to change these depressing statistics. ■

CME Questions

1. Although rare, the risk of angioedema is how much more common with ACEIs than beta-blockers?
   a. 15%
   b. 50%
   c. 100%
   d. 300%

2. Among Medicare patients, which is correct regarding therapy of atrial fibrillation?
   a. Warfarin use decreased with increasing CHADS2 score.
   b. Amiodarone was the most frequently prescribed antiarrhythmic agent.
   c. The rate control strategy was more frequently used as age increased.
   d. All of the above

3. In a large Canadian study, the 1-year hemorrhage rate on warfarin for atrial fibrillation was:
   a. 1%.
   b. 2%.
   c. 4%.
   d. 8%.

4. A study of reprogramming ICDs to reduce inappropriate shocks resulted in which surprising finding?
   a. Increased antitachycardia pacing
   b. Increased appropriate shocks
   c. Reduced mortality
   d. Reduced syncope

5. In patients aged older than 60 years, selecting CABG rather than PCI resulted in:
   a. lower mortality.
   b. more repeat revascularization.
   c. fewer strokes.
   d. lower costs.

6. Comparing women to men with regard to PCI outcomes showed that women have higher:
   a. procedural success rates.
   b. adjusted survival rates.
   c. MI rates.
   d. bleeding rates.

CME Objectives

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

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.

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.*

Zolpidem and Risk of Falls in Hospitalized Patients

In this issue: Zolpidem and risk of falls; AVR and anticoagulation; statins in cancer patients; and FDA actions.

Zolpidem and risk of falls

Zolpidem (Ambien) increases the risk of falls in inpatients, according to a new study from the Mayo Clinic. The records of hospitalized patients who were not in the intensive care unit were reviewed in this retrospective cohort study. The rate of falls was compared in those who were administered zolpidem vs those for whom it was prescribed but not administered. After controlling for age, gender, insomnia, delirium, dose of zolpidem, Charlson comorbidity index, Hendrich's fall risk score, length of stay, visual impairment, gait abnormality, dementia/cognitive impairment, and concomitantly administered meds, the rate of falls was four times higher in those administered zolpidem (n = 4962) vs those who were prescribed but did not receive zolpidem (adjusted odds ratio 4.37, 95% confidence interval [CI], 3.34-5.76; $P < 0.001$). The authors conclude that zolpidem was a strong, independent, and potentially modifiable risk factor for inpatient falls. The authors suggest that changing order sets so that zolpidem use is not encouraged could potentially reduce fall rates in hospitalized patients. They also suggest that there is limited evidence to recommend other hypnotic agents as safer alternatives (*J Hosp Med* published online Nov. 19, 2012. doi: 10.1002/jhm.1985). ■

Anticoagulation and AVR

Bioprosthetic valves are preferred to mechanical valves for aortic valve replacement (AVR) in the elderly because of lack of need for anticoagulation in the long-term, but short-term anticoagulation is required. The duration of anticoagulation after valve replacement has been unclear. Now, a new study from Denmark suggests 6 months is optimal. Using the Danish National Patient Registry, more than 4000 patients who had a bioprosthetic AVR between 1997 and 2009 were identified. Rates of stroke, thromboembolic events, cardiovascular death, and bleeding were assessed along with warfarin treatment duration. Rates of events per 100 person-years in patients not treated vs those treated with warfarin for 3 months were 7 vs 2.7 for stroke, 13 vs 4 for thromboembolic events, 11.7 vs 5.4 for bleeding, and 32 vs 3.8 for cardiovascular death. The rate of cardiovascular death was 6.5 vs 2.0, favoring warfarin from 90 days to 179 days. The authors conclude that stopping warfarin within 6 months of bioprosthetic AVR surgery was associated with increased cardiovascular death. These findings challenge the current guidelines that recommend 3 months of antithrombotic treatment after AVR surgery suggesting that "patients will gain from an additional 3 months of warfarin treatment in terms of reduced cardiovascular death without risking significant increase in bleeding events" (*JAMA* 2012;308:2118-2125). An accompanying editorial states that this study provides important information to help clinicians understand the benefits and risks of warfarin use after bioprosthetic aortic valve implantation, but it

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

does not address the issue of adjunctive aspirin or the role of new novel oral anticoagulants (*JAMA* 2012;308:2147-2148). ■

Statins in patients with cancer

Patients taking a statin when diagnosed with cancer have a better prognosis than patients who are not taking statins, according to a new study. This study also used the Danish Registry in which all patients with a cancer diagnosis between 1995 and 2007 were evaluated. Roughly 19,000 patients were on a statin prior to diagnosis and 277,000 were not. Those taking statins were 15% less likely to die of any cause and 15% less likely to die of cancer (hazard ratio 0.85, 95% CI, 0.82-0.87 for cancer). The benefit was present regardless of statin dose or cancer type. The authors suggest that this is biologically plausible since cholesterol is needed for cell proliferation. They suggest "a need for trials of statins in patients with cancer" (*N Engl J Med* 2012;367:1792-1802). Previous studies have suggested reduced cancer mortality with statins in patients with prostate cancer and reduced recurrence rates in breast cancer patients. ■

FDA actions

The FDA has concluded a safety review of dabigatran (Pradaxa) and found that the drug is not associated with more serious bleeding events than warfarin. The review was done using insurance claims and data from the FDA's Sentinel Initiative. According to the FDA, the bleeding rates are consistent with the observations from large clinical trials, including RE-LY, which showed that bleeding rates in patients newly started on dabigatran were similar to rates associated with new use of warfarin. Therefore, the FDA has not changed its recommendation regarding dabigatran (FDA Drug Safety Communication, Nov. 2, 2012). The next day, *The New York Times* published an article reporting that dabigatran has been associated with more than 500 deaths in the United States since it was introduced. It also detailed several tragic cases of bleeding deaths associated with the drug. The article indicts the FDA stating "… the approval process was not sufficiently rigorous because it allowed a potentially dangerous drug to be sold without an option for reversing its effects." The article also mentions more than 100 lawsuits that have been filed in federal courts "…and thousands more are expected" (*The New York Times* Nov. 3, 2012:B1).

The FDA has expanded the approval of rivaroxaban (Xarelto) to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), both for acute treatment and prevention of recurrence. The drug is already approved for prevention of DVT and PE after knee and hip replacement surgery and for prevention of stroke in patients with non-valvular atrial fibrillation. It is the first oral drug approved to treat DVT and PE since warfarin was approved 60 years ago; but unlike warfarin, rivaroxaban can be used as monotherapy from diagnosis until treatment is discontinued. Approval was based on three studies of nearly 9500 patients with DVT or PE randomized to rivaroxaban, enoxaparin/vitamin K antagonist, or placebo. Rivaroxaban was equivalent to enoxaparin/vitamin K antagonist and superior to placebo for preventing recurrent DVT or PE.

The FDA has approved a new egg-free flu vaccine for adults. The vaccine is manufactured using cultured mammalian cells instead of fertilized chicken eggs. The manufacturer claims that the cell culture technology enables a rapid response to public health needs, such as a pandemic, since cell culture technology allows vaccines to be manufactured within weeks as opposed to traditional flu vaccines that depend on a large number of fertilized chicken eggs to grow the virus. Cell culture technology is used for several other vaccines including polio, rubella, and hepatitis A vaccines. Approval was based on a randomized, controlled clinical study of 7700 adults ages 18-49. The new vaccine was 83.8% effective in preventing influenza when compared to placebo. Injection site reactions are the most common side effects. The new vaccine is marketed as Flucelvax by Novartis.

The FDA has approved the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib, dosed orally twice a day, is approved for RA patients who have failed methotrexate. The drug will compete with the parenteral RA drugs adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Tofacitinib carries a boxed warning regarding the increased risk of opportunistic infections, tuberculosis, cancers, and lymphoma; increases in cholesterol and liver enzymes; and decreases in blood counts. Approval was based on seven clinical trials in which the drug showed improvements in clinical response and physical function compared to placebo in patients with moderate-to-severe RA. Tofacitinib will be marketed by Pfizer as Xeljanz. The cost is projected to be just over $2000 per month, similar to other non-methotrexate biologic treatment options. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Gabapentin for Chronic Cough

Source: Ryan NM, et al. Gabapentin for refractory chronic cough: A randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380:1583-1589.

Chronic undifferentiated cough — that is, cough without any readily visible explanation such as upper respiratory infection, lower respiratory infection, pulmonary lesion, heart failure, etc. — usually turns out to be one of three entities: post-nasal drip, asthma, or acid reflux. Indeed, empirically trying meds for such maladies usually resolves the cough. Nonetheless, despite exhaustive investigation, some patients remain with cough of undetermined etiology, at which point the treatment is problematic.

It has been suggested that chronic cough might reflect a central neural sensitization process that has some pathologic similarities to neuropathic pain. Since gabapentin works well for neuropathic pain, could it also have a positive effect on chronic cough?

Ryan et al studied a population of patients with chronic cough (n = 62) in whom secondary causes (e.g., infection, reflux, asthma) had been eliminated. Study subjects were randomized to gabapentin (up to 1800 mg/d) or placebo for 10 weeks.

At the end of the trial, gabapentin improved cough-related quality of life more than placebo and was well tolerated. Considering that in neuropathic pain trials the dose of gabapentin has been up to twice as high (3600 mg/d), it is reassuring to note that moderate gabapentin doses provide clinically relevant cough improvements. In an era of closer scrutiny applied to use of opioids, another alternative for chronic undifferentiated cough is welcome. ■

Can Statins Reduce Cancer-Related Mortality?

Source: Nielsen SF, et al. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;367:1792-1802.

It is generally believed that the primary mechanism of statin-related cardiovascular (CV) risk reduction is achieved through reductions in LDL. That statins might have other pleiotropic actions, such as plaque stabilization, is the subject of much controversy. Recently, recognition of the impact of statins on new-onset diabetes (a relative 9% greater risk than non-statin users) has given reason for pause. For secondary prevention, the risk-benefit ratio is prominently positive for statin therapy, but much less convincing for primary prevention. A similar picture is emerging in reference to aspirin in CV prophylaxis.

Reminiscent of the aspirin story (i.e., even though primary prevention with aspirin has never been shown to reduce mortality, the favorable effects on CV events — when combined with recently recognized cancer risk reduction — sweetens the deal), we are presented now with the suggestion that statins also reduce cancer-related mortality.

Nielsen et al report on a large dataset of Danish patients who had a diagnosis of cancer (n = 295,925) over the 1995-2007 interval. A comparison was made between statin never users (n = 277,204) and statin users (n = 18,721) with respect to overall and cancer-related mortality.

Statin users had a 15% relative risk reduction for cancer-related death when compared to non-users. Thirteen different cancer types were specified, each of which demonstrated similar benefit. The authors suggest that the cholesterol synthesis-limiting effects of statins may disrupt cancer cell membrane stability and cellular processes, leading to the beneficial observed effects. ■

Are All of Those Multivitamin Dollars Well Spent?

Source: Sesso HD, et al. Multivitamins in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. *JAMA* 2012; 308:1751-1760.

Americans have been depicted as an overly pill-happy lot, much more motivated to take a statin than incorporate dietary change for cholesterol, or take a sulfonylurea rather than exercise and lose weight to improve their diabetes, etc. For a while, the idea of multivitamins seemed like a no-lose proposition; after all, few of us were keeping track of the amounts of essential nutrients we ingest, so multivitamins appeared to provide, at worst, an innocent and inexpensive nutrient insurance policy.

In an era in which essential nutrient deficiency is a stark rarity, the use of vitamin and nutrient supplements is increasingly called into question.

The Physicians' Health Study II is a controlled trial of adult (age > 50 years) male U.S. physicians (n = 14,641) randomized to a daily multivitamin or placebo.

Over a follow-up period of (median) 11.2 years, there was no discernible difference between placebo and a daily multivitamin on CV events, stroke, or mortality.

A parallel "sister study" from the Physicians' Health Study reported a week later in *JAMA* had slightly more encouraging news: Within the same population as mentioned above, the risk of total cancer was reduced by 8% in multivitamin users. Although the risk reduction for cancer was small, and the *P* value only marginally significant, for clinicians who would advocate for multivitamins in the face of failed CV data, the cancer outcomes are modestly more sanguine. ■

Relapsing Lyme Disease: Fact or Fiction?

Source: Nadelman RB, et al. Differentiation of reinfection from relapse in recurrent Lyme disease. *N Engl J Med* 2012;367:1883-1890.

A characteristic dermatologic manifestation of the acute phase of Lyme disease (LYME) is erythema migrans. With appropriate antibacterial treatment of LYME, the etiologic bacterium *Borrelia burgdorferi* is typically eradicated, and further disease progression is prevented. Untreated LYME can induce repetitive episodes of erythema migrans, as can LYME treated with antibiotics to which *B. burgdorferi* is not susceptible. In an individual patient, it may be difficult to differentiate disease relapse from new infection with a different strain of *B. burgdorferi*.

Genotyping of *B. burgdorferi* surface proteins allows determination of specific bacterial subtypes. Nadelman et al performed such analysis on patients (n = 17) who had experienced two episodes of erythema migrans. Each of the patients had received appropriate antibacterial treatment.

The second episode of erythema migrans was not caused by the same strain of *B. burgdorferi* in any of the patients, indicating that in each circumstance the patient had suffered reinfection rather than relapse. Whereas clinicians may have suspected relapse in patients with repeated episodes of LYME, it appears that reinfection with a new strain is more likely to be responsible. ■

Hypertension and Gout

Source: McAdams-DeMarco MA, et al. Hypertension and the risk of incident gout in a population-based study: The atherosclerosis risk in communities cohort. *J Clin Hypertens* 2012;14:675-679.

Gout and hypertension are often seen together. Indeed, there has been a substantial degree of discussion about the potential for elevated levels of uric acid to cause hypertension. The "storyline" remains incomplete, however, because of the observational nature of the data, confounders like thiazide diuretics (which of course elevate uric acid in treated hypertensives), and renal insufficiency, which is common in hypertension and is also associated with elevated uric acid. If uric acid is ultimately proven to increase the incidence of hypertension, it will still remain to be determined whether lowering urate can reduce hypertension safely and effectively.

The Atherosclerosis Risk in Communities study (ARIC) study population provides a dataset for evaluating the association between gout and hypertension. Adults (n = 15,792) from four different metropolitan areas were followed for approximately 10 years.

There was a strong relationship between gout and hypertension. Participants with hypertension were almost two to three times as likely to develop gout, even after adjustment for confounders. For instance, when results were evaluated only among persons not taking thiazide diuretics, a positive association between hypertension and gout was still found. The authors posit that the relationship between hypertension and gout is mediated through blood pressure-induced renal damage that leads to increased levels of uric acid. ■

Zoledronic Acid Treatment of Osteoporosis in Men

Source: Boonen S, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *N Engl J Med* 2012;367:1714-1723.

When hearing the word osteoporosis, most clinicians think "pink," as if the disorder only affected women. To the contrary, 30% of hip fractures occur in men, and the post hip-fracture mortality in men is higher than women. Although the dataset about preferred treatments is less robust for men than women, trials of oral bisphosphonates have been shown to provide meaningful fracture risk reduction for men and women.

Zoledronic acid (ZOL) is a parenterally administered bisphosphonate that has been previously demonstrated to provide significant reduction in osteoporotic fractures in women. For treatment of osteoporosis, ZOL is administered as a single intravenous dose, repeated in 1 year.

Boonen et al performed a placebo-controlled randomized trial in osteoporotic men (n = 1199). As in most osteoporosis trials, calcium (1000-1500 mg/d) and vitamin D (800-1200 IU/d) supplements were administered in both the treatment and placebo arms of the study. The primary outcome variable of the study was new vertebral fractures.

At the end of the 2-year study, men who had received ZOL enjoyed a 67% relative risk reduction in new vertebral fractures (1.6% vs 4.9%), as well as improved bone mineral density. There were no serious drug-related adverse events. Risk for osteoporotic vertebral fracture in men is promptly and effectively reduced by zoledronic acid. ■

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