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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Transcatheter Aortic Valve Implantation vs Surgical AVR for Severe Aortic Stenosis

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco
Dr. Boyle reports no financial relationship relevant to this field of study.

SOURCE: Smith C, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187-2198.

Percutaneous transcatheter aortic valve implantation (TAVI) is an emerging technique for the treatment of aortic stenosis (AS). By this method, a bioprosthetic valve (bovine pericardium) attached to a stent can be deployed in the aortic valve position via a catheter delivery system inserted through either the femoral artery or via the apex of the left ventricle. This technique is available in Europe and is being considered by the FDA for release in the United States. The previously presented Partner Trial Cohort B demonstrated a 20% reduction in mortality with TAVI compared to medical therapy in patients with inoperable severe AS. However, in patients who are still candidates for surgical aortic valve replacement (AVR), it is not known whether TAVI is a reasonable alternative. The Partner Trial Cohort A, presented here by Smith et al, is a randomized, multicenter trial comparing TAVI vs AVR in high-risk patients with severe symptomatic AS. The study was designed to demonstrate noninferiority of TAVI compared to AVR and the primary endpoint was all-cause mortality at 1 year.

The study was performed in 25 centers in three countries, but predominantly in the United States. The authors enrolled 699 patients with severe AS (defined as aortic valve area < 0.8 cm^2 plus either a mean gradient ≥ 40 mmHg or a peak velocity of at least 4.0 m/sec) and randomized them to surgical AVR (n = 351) vs TAVI (n = 348). All patients were

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deemed to be at high risk by the regional surgeon, guided by an estimated post-operative mortality of at least 10% by the STS (Society of Thoracic Surgeons) scoring system. Exclusion criteria were a bicuspid or non-calcified valve, coronary artery disease requiring revascularization, a left ventricular ejection fraction of less than 20%, an aortic annulus diameter of < 18 mm or > 25 mm, severe (4+) mitral or aortic regurgitation, a recent neurologic event, and severe renal insufficiency. Patients assigned to TAVI underwent transfemoral placement (n = 248), unless there was significant peripheral arterial disease (PAD) that precluded large sheath placement in which case they underwent a trans-apical procedure (n = 103). All patients received heparin during the procedure and dual antiplatelet therapy for 6 months post-procedure.

This study enrolled high-risk patients but there were no differences between groups at baseline. The mean age was an astonishing 84 years and the mean STS score was 11.8%. Ninety-four percent of patients were in NYHA class III or IV. After randomization, 42 patients did not undergo the assigned procedure (4 in the TAVI group and 38 in the surgical AVR group). The TAVI procedure was aborted or converted to an open procedure in 16 of 348 patients (4.6%) and surgical AVR was converted to TAVI in one case.

At 1 year, there was no difference in mortality following TAVI vs surgical AVR. The all-cause mortality rate was 24.2% in the TAVI group and 26.8% in the surgical AVR group ($P = 0.44$), an absolute reduction of 2.6% in the TAVI group. This was within the authors' predefined margin of 7.5% for noninferiority ($P = 0.001$ for noninferiority). The rates of major stroke were 3.8% in the TAVI group and 2.1% in the surgical AVR group at 30 days ($P = 0.20$) and 5.1% and 2.4%, respectively, at 1 year ($P = 0.07$). At 30 days, major vascular complications were significantly more frequent with TAVI (11.0% vs 3.2%; $P < 0.001$); adverse events that were more frequent after surgical replacement included major bleeding (9.3% vs 19.5%; $P < 0.001$) and new-onset atrial fibrillation (8.6% vs 16.0%; $P < 0.01$). More patients undergoing TAVI had an improvement in symptoms at 30 days, but by 1 year, there was not a significant between-group difference.

At 1 year, TAVI was slightly superior to surgical replacement with respect to the mean aortic-valve gradient (10.2 ± 4.3 mmHg vs 11.5 ± 5.4 mm Hg; $P = 0.008$) and mean valve area (1.59 ± 0.48 cm^2 vs 1.44 ± 0.47 cm^2; $P = 0.002$), although the clinical significance of such small differences remains unknown. Moderate or severe paravalvular regurgitation was more frequent in the TAVI group than in the surgical group at 30 days (12.2% vs 0.9%; $P < 0.001$) and at 1 year (6.8% vs 1.9%; $P < 0.001$). The authors conclude that in high-risk patients with severe AS, TAVI, and surgical AVR were associated with similar rates of survival at 1 year, although there were important differences in periprocedural risks.

■ COMMENTARY

This landmark trial demonstrates that percutaneous TAVI is a realistic alternative to surgical AVR in high-risk patients with severe symptomatic AS. It is worth noting that the predicted 30-day surgical mortality was 11.8%, but the observed mortality was 8.0% in those who underwent surgical AVR. This suggests that the surgeons involved in this trial were very skilled, and yet TAVI still performed well compared to such skilled surgery.

There are important periprocedural complications that warrant mention. Vascular access complications are more common with TAVI than with surgical AVR. Although these may sound like minor complications, they can be more severe than most cardiac catheterization-related access site complications due to the large sheath sizes. As experience with the procedure has grown, and the devices are becoming smaller, access site complications are becoming less frequent, and we can expect the rates to continue falling as devices and techniques continue to evolve. Furthermore, there was a numerically higher rate (double) of stroke in the TAVI group. The rates were higher in both the transfemoral and the transapical groups. Hopefully this rate declines as the devices become lower in profile and with newer embolic protection devices that are being developed. Further research is needed to reduce this stroke risk if TAVI is to become a permanent part of the treatment landscape for AS. We look forward to further data from this trial that will involve cost-effectiveness analyses.

The future for percutaneous aortic valve therapies looks bright. The FDA is currently considering approval for this device, and another percutaneous aortic valve is in phase 3 clinical trials. Numerous iterations of devices are in early-phase testing and, in the years to come, there will likely be significant improvements over the generation of devices currently used in Europe. However, for now, surgical AVR remains the standard of care for patients in the United States with severe AS. ■

ABSTRACT & COMMENTARY

Cardiac Rehab Improves Outcomes After Percutaneous Coronary Intervention

By Andrew J. Boyle, MBBS, PhD
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SOURCE: Goel K, et al. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation* 2011;123:2344-2352.

The benefits of cardiac rehabilitation following myocardial infarction (MI) are well known. However, whether these benefits are also seen in ambulant community-based patients who undergo percutaneous coronary intervention (PCI) is not known. Goel and colleagues examined the Mayo Clinic PCI database for patients who resided in Olmsted County, Minnesota, who underwent PCI between 1994 and 2008; they compared the outcomes of those who attended cardiac rehabilitation (CR) following PCI against those who did not. Their primary endpoint was all-cause mortality.

They identified 2395 patients, of whom 964 (40%) participated in at least one CR session within 3 months of PCI. Interestingly, after the Centers for Medicare and Medicaid changed the regulations to include PCI as a reimbursement indication for CR in 2006, there was an approximate 3-fold increase in the rates of attendance at CR. The mean number of sessions attended was 13 per patient; however, they included in their analysis all patients who attended one or more sessions as having received CR. Independent factors that were positively associated with CR participation include age, year of PCI, history of acute MI, involvement of minor branches of the coronary artery, antiplatelet therapy during PCI, and occurrence of in-hospital MI or coronary artery bypass graft surgery. On the other hand, smoking, history of diabetes mellitus, previous PCI, and use of drug-eluting stents were independently associated with decreased participation in CR after PCI. To assess the effect of CR on clinical outcomes, the authors used three different statistical techniques to enhance the accuracy of their results: propensity score-matched analysis (n = 1438), propensity score stratification (n = 2351), and regression adjustment with propensity score in a 3-month landmark analysis (n = 2009). Significant baseline differences existed between those who received CR and those who did not receive CR, but after propensity score matching, there were no clinical differences between groups.

CR was associated with a significant 45%-47% reduction in all-cause mortality by all three statistical analyses (HR 0.53 to 0.55; $P < 0.001$). However, there were no differences in the rates of non-fatal MI and repeat revascularization. There was a trend toward reduction in cardiovascular mortality (significant reduction by one statistical method but non-significant by the other two methods). The authors conclude that CR participation after PCI was associated with a significant reduction in mortality rates and these findings add support for current guidelines, practice standards, and insurance coverage policies that recommend CR for patients after PCI.

■ COMMENTARY

Goel and colleagues present an important dataset that advances our knowledge of the effects of CR on patients who have undergone PCI. Several strengths and limitations of the study bear discussing. Because their center was the only CR facility in the county during the time of the study, and they only included patients residing in their county, their data are likely to be inclusive. This cohort has been well studied and is representative of other community cohorts. However, they are a predominantly white, non-hispanic community, and so the results here may not be generalizable to more racially heterogeneous communities.

Another important factor to consider is the retrospective observational nature of this study. Although these data are collected prospectively, one

must interpret retrospectively analyzed data with caution. There is likely to be inherent selection bias in who is referred for CR, as well as who actually attends. There are obvious confounders that were not collected in this dataset, such as education level and socioeconomic status, that are known to influence outcomes in patients with coronary artery disease. Although the rigorous statistical methodologies used by the authors strengthen their conclusions from these data, there will always be unmeasured confounders in non-randomized studies, and the results should be interpreted with this in mind.

The mechanism of this mortality reduction is not addressed in this study, and one is left to ponder the mechanism underlying such a large reduction in all-cause mortality, despite no reduction in cardiovascular mortality and no reduction in MI. CR may have physiological benefits for many organ systems, not just the heart, and may result in lower mortality from other disease states. This finding is, however, consistent with prior studies. This study confirms that CR is an important part of our treatment of patients with coronary artery disease who have undergone PCI. ■

ABSTRACT & COMMENTARY

How to Measure Blood Pressure — Again

By Michael H. Crawford, MD, Editor

SOURCES: Powers BJ, et al. Measuring blood pressure for decision making and quality reporting: Where and how many measures? *Ann Intern Med* 2011;154:781-788; Appel LJ, et al. Improving the measurement of blood pressure: Is it time for regulated standards? *Ann Intern Med* 2011;154:838-839.

New emphasis on optimal medical therapy in atherosclerotic cardiovascular (CV) disease has focused attention on the short-term variability of blood pressure (BP) measurements and the difficulty this poses for the diagnosis and treatment of hypertension. The availability of home BP monitors adds complexity to the problem, as no guidelines exist for their use. Thus, these investigators from the Durham Veterans Affairs Medical Center compared home, clinic, and research systolic blood pressure (SBP) measurements in 444 patients with hypertension who were part of a study to test the efficacy of BP management by nurses over the phone using home BP telemetry.

In this study, BP was measured by three methods: nurse measurements at routine clinic visits; two research clinic measurements 6 months apart for 18 months; and at least three home measurements a week for 18 months. For each measurement method, the mean within patient coefficient of variation in SBP (SD/mean SBP) was calculated. The patients were almost all men (92%), half were black, mean age was 64 years, and most had hypertension for > 10 years. More than 111,000 BP measurements were analyzed: 7121 clinic, 3218 research, and 100,842 home. SBP control was defined as < 140 mmHg for clinic and research measurements and < 135 mmHg for home measurements. Control varied considerably: 28% clinic, 47% home, and 68% research. Short-term variability (30 days clinic, 90 days home) was similar for all three measurements at about 10%.

Comparing measurement methods, 52% of patients had a mean clinic BP ≥ 10 mmHg higher than their mean home BP. Within patient variance decreased with the number of measurements using all three methods. The greatest reduction in variance occurred with going from one to two measurements and decreased rapidly thereafter plateauing at four to six measurements. The number of measurements required by all three methods depends on the measured SBP. For example, a patient with one clinic value of 132 mmHg has a 40% probability of having a true SBP of > 140 mmHg; whereas a patient with a single measurement of 150 mmHg has a 70% probability of a true SBP > 140 mmHg. The authors concluded that the average of several measurements are more accurate than one clinic measurement of SBP.

■ COMMENTARY

Managing hypertension in many of our CV disease population is a challenge in many patients. One source of the difficulty is the variability in BP measurements in individual patients. The other major source is the difference between home and clinic BPs. The uncertainty about BP measurements is a common reason physicians are reluctant to change a patient's medicines. Adding more medication for high clinic pressures which are spuriously high may lead to hypotension, syncope, renal failure, myocardial ischemia, and a vicious cycle to hospital admission or death in the worst case scenario. A better way to determine a patient's true BP would be welcome. This study addresses this issue.

They document a 10 mmHg difference between clinic BPs and home BPs, which also has been shown in previous studies. The editorial accompanying this paper suggests that this may be due in part to the casual approach to BP measurement techniques in many clinics. In this study, SBP control was found in 68% of the patients on the research clinic measurements, 47% of the home measurements, and 28% of the clinic measurements. Although some of these discrepancies may be due to white coat effect in clinic, the difference in home vs research clinic suggests that poor technique probably plays a role. As the editorial points out, the American Heart Association had published guides for measuring BP properly since 1939, apparently to no avail. This is truly a sad state of affairs and should be addressed immediately by us all.

Variability within the patient occurs over hours to days, so multiple measurements of BP in clinic will not solve this problem. Also, the problem plagued all three measurement techniques to the same extent. This study suggests that the average of repeated measures on different days is the best way to improve accuracy. The JNC recommends two separate BP measurements on different days. This study shows that two measures will give you the biggest increment in SBP accuracy but 5-6 measures increase accuracy maximally unless SBP is near 140 mmHg, then 10 measurements are necessary. These data suggest that home BPs are the best way to achieve accuracy, since it is impractical to have the patient return to clinic 5-10 times in many situations. Unfortunately, the instruments are expensive and some patients do not have the wherewithal to measure their own BP. Accommodating these patients is difficult, but could be achieved by home visits, or multiple visits to a non-physician provider, or a home telemetry device that does not require a high level of patient interaction. ■

ABSTRACT & COMMENTARY

Aspirin for Primary Prevention

By Michael H. Crawford, MD, Editor

SOURCE: Bartolucci AA, et al. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol* 2011;107: 1796-1801.

The use of aspirin for the primary prevention of cardiovascular (CV) disease remains controversial. In this publication, Bartolucci updates his 2006 meta-analysis by adding three new trials to the six previous ones. Since aspirin may have different effects on different CV diseases, the data were classified into several outcomes of interest compared in almost 51,000 subjects on aspirin and more than 49,000 on placebo. Individually, only two trials showed a significant decrease in CV mortality, but each trial was significant for at least one CV endpoint. For example, the Women's Health Study (WHS) was significant for stroke reduction only. The nine-trial combined results showed a decreased risk of myocardial infarction (MI; $P = 0.042$) and total CV events ($P = 0.001$, CV death, MI, and stroke). There was significant heterogeneity across trials in total coronary heart disease ([CHD] MI and death due to CHD $P = 0.001$ and MI $P = 0.004$). The combined hazard ratios for six different endpoints ranged from 0.813 to 0.956 in favor of aspirin for risk reductions of 4.4% to 18.7%. Only non-fatal CHD events, total CHD, and the combined endpoint of CV death, MI, and stroke were reduced > 10%. Stroke reduction was 8.1%, CHD mortality was 4.4%, and all-cause mortality was reduced 5.5%. The authors concluded that aspirin decreases the risk of CV events and MI, but not stroke, nor any CV cause of death or total mortality.

■ COMMENTARY

I hate it when healthy people ask me if they should take an aspirin a day because I do not have the answer to this simple question. Thus, I read this latest meta-analysis with high expectations that I would get the answer. So imagine my disappointment that this question still does not have a clear answer. This analysis of nine primary prevention trials included two new trials that studied diabetics without symptomatic vascular disease. The inclusion of diabetics could mean more events and a greater chance to see differences in these higher risk subjects. Disappointingly these studies in diabetics showed that some outcomes were worse on aspirin, including CHD mortality.

The overall analysis showed a reduction in coronary events, but not stroke. No mortality endpoint was significantly reduced. This has

always bothered me — how can an event be reduced, but the mortality from it not? Are such results important? Also in this analysis, the percent reductions in outcomes varied from 4% to 18%. When you weigh in the risk of gastrointestinal bleeding, even the authors admit that the net benefit is uncertain.

Despite including nine trials, almost 60% of the subjects came from the WHS and the Hypertension Optimal Treatment (HOT) study. The WHS was only positive for a reduction in stroke in older women. HOT showed reduced events, but not mortality, and overall was closer to the results of the meta-analysis. Based on these two studies, it has been concluded that aspirin prevents stroke in women and heart attack in men, but it is not as simple as that in the overall results of this meta-analysis.

What this analysis does not provide is any breakdown of the results by age, sex, or risk profile of the subjects, nor the dose of aspirin. If we are going to individualize therapy, we need to know these variables. Since there is no strong message from this analysis, therapy will need to be individualized. Also, most of these studies included only middle-aged or older subjects, but what age do we start recommending aspirin? Based on many studies, aspirin is clearly indicated for secondary prevention of all vascular disease patients, and probably for those who probably have vascular disease based on their risk profile, but not necessarily diabetics unless they have a high-risk profile. For the true primary prevention group of low-to-intermediate risk subjects, aspirin prophylaxis probably should not be considered until age 45 in men and 55 in women since vascular events are unusual before those ages and the risks of bleeding would outweigh the potential benefit. In the older subjects at low risk — I leave the decision to the subject and if they choose to take aspirin — I recommend 81 mg of the enteric coated type. You can make a better case for the intermediate-risk patient, but we do not know if just vigorously controlling their risk factors would be enough. This type of comparative effectiveness study of aggressive risk factor control plus or minus aspirin has not, and probably will not be done, so we can only speculate on the results. ■

ABSTRACT & COMMENTARY

Sudden Death Post Myocardial Infarction

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

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

SOURCE: Ye S, et al. Circumstances and outcomes of sudden unexpected death in patients with high-risk myocardial infarction: Implications for prevention. *Circulation* 2011;123:2674-2680.

In this paper, the authors present data from the Valsartan in Acute Myocardial Infarction Trial (VALIANT) on the circumstances and outcomes of cardiac arrest after myocardial infarction (MI). VALIANT was a double-blind, randomized, controlled trial that assessed treatment with valsartan, captopril, or both in more than 14,000 patients after an acute MI that had been complicated by heart failure and/or left ventricular systolic dysfunction. All deaths in VALIANT were reviewed by a central-blinded adjudication committee and patients having episodes of cardiac arrest with successful resuscitation or sudden cardiac death were included in this trial. Patients who underwent ICD implantation during the acute hospitalization (n = 94) were excluded.

Among the 14,609 patients enrolled in VALIANT, 1067 experienced sudden death or resuscitated cardiac arrest (903 deaths and 164 successful resuscitations). In addition, there were 1486 nonsudden cardiovascular deaths and 385 noncardiovascular deaths. Risk factors for sudden death or cardiac arrest included the following: advanced age; higher systolic and diastolic baseline blood pressures; higher baseline heart rates; higher Killip class; lower left ventricular ejection fractions; higher rates of diabetes, hypertension, and prior MI; and a lower likelihood of treatment with percutaneous intervention, thrombolytics, beta adrenergic blockers, or amiodarone. Among the 1067 patients who had sudden death or cardiac arrest, 251 (24%) had an event within the first 40 days of their index MI, 140 patients had their event between 41 and 90 days after index MI, and 671 had an event more than 90 days after index MI. The initial ECG rhythm at the time of cardiac arrest was available for 283 of the 1062 patients and included ventricular tachycardia or ventricular fibrillation in 189 patients (67%), asystole in 59 patients (21%),

and pulseless electric activity in 17 patients (6%). Symptoms were reported to precede the arrest in 46% of patients in whom the data were available. Most sudden deaths occurred at home. Among the 978 sudden death events where the arrest location was known, 645 (66%) occurred at home, 204 (21%) occurred in hospital, and 129 (13%) occurred outside the home but not in hospital. In-hospital sudden death was more common within the first 40 days after MI with most of the later events occurring in the home. Among those patients with sudden death events at home, activity was known for 269 of 645 patients. Of these, 139 (52%) were asleep at the time of the event and 130 (48%) were awake when the event occurred. Events during sleep were witnessed in only 19% of cases compared to 70% of events in awake patients. In the subgroup of patients who were resuscitated from a cardiac arrest, ICD implantation was associated with improved survival.

The authors conclude that sudden death after complicated MI is relatively common (7% at about 2 years) and it occurs most frequently at home with preceding symptoms or during sleep.

■ COMMENTARY

Sudden death in the early phases after an acute MI remains a major clinical problem. Revascularization when possible and various pharmacologic strategies have been shown to be effective and should be routinely employed. Early, within 40 days post infarct, ICD therapy has been tested in several trials (IRIS and DINAMIT) and has been shown not to improve survival. As a result, early ICD implantation after infarction is specifically not allowed under Medicare guidelines in the United States. At-home automatic external defibrillator use also has been tested in a randomized trial (HAT), and this too was shown not to be effective. The data presented here about the epidemiology of post infarction sudden death are interesting and should cause cardiologists to reexamine their practices with post MI patients. About half of the cardiac deaths are sudden. The majority of the sudden deaths occur more than 40 days after infarct and the mechanisms of death appear to be amenable to intervention with an ICD. If these patients had been routinely screened for persistent risk at the 40 day time point, it is likely that the sudden death mortality could have been reduced substantially. ■

ABSTRACT & COMMENTARY

Relationship of Lifestyle Risk Factors to Sudden Death

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

SOURCE: Chiuve SE, et al. Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women. *JAMA* 2011;306:62-69.

This paper presents data from the Nurses' Health Study. This is a large study that was begun in 1976 which surveyed nurses with initial ages between 30 and 55 and collected data on lifestyle and other risk factors and correlated these data with the development of cardiac disease. In this study, data from the 1984 survey were used as the baseline for analysis. The study collected data biannually that included smoking status, body weight, use of medications, menopausal status, and physician diagnosis of disease. Physical activity was assessed every 2 to 4 years using a validated questionnaire. Diet was assessed using a validated food frequency questionnaire that was filled out every 4 years. In this paper, the authors considered the relationship of four lifestyle factors: smoking, exercise, diet, and weight to the incidence of sudden cardiac death (SCD). Most of the data presented consider these findings in a binary fashion as either high or low. Low-risk categories included physical activity of 30 minutes per day or longer, a body mass index of 25 or less, an alternate Mediterranean diet score in the top 40% of the cohort distribution, and no current smoking. Mortality data were collected through medical records, autopsy reports, and interviews with next of kin. Cardiac deaths were considered sudden if the death or cardiac arrest occurred within 1 hour of symptom onset and was not associated with evidence of circulatory or neurologic impairment before death. Unwitnessed and unexpected deaths were considered to be sudden deaths.

During 26 years of follow-up, there were 321 cases of SCD. Nonsmokers, those who exercised regularly, and those adhering to a Mediterranean diet had a lower risk of sudden death. The association between BMI was J shaped with a nadir in sudden death risk among women with a BMI of 21 to 24.9. When the four risk factors (smoking, diet, exercise, and weight) were combined as binary values in a lifestyle assessment, the total score was inversely associated

with the risk of sudden death. For women with no low-risk factors, the sudden death rate was 22 cases per 100,000 person years. With 1, 2, 3, and 4 low-risk factors, the rates were 17 cases (score 1), 18 cases (score 2), 13 cases (score 3), and 16 cases per 100,000 patient years (score 4). For the individual factors, the relative risk for nonsmoking was 0.5, for frequent exercise was 0.62, for the Mediterranean diet was 0.69, and for BMI less than 25 was 0.8. In the entire cohort, the percentage of population attributable risk for sudden death associated with these four lifestyle factors was 81%.

The authors acknowledge that their data can be strictly applied only to highly educated white female health professionals and may not be generalizable to men or women of other ethnicities or socioeconomic status. However, identifying these lifestyle factors provides the basis for a sudden death prevention strategy.

■ COMMENTARY

This paper identifies four potentially modifiable risk factors for sudden death in middle-aged women. These risk factors also are linked to the development of hypertension and ischemic heart disease and may not be specific for sudden death itself. However, these four factors are modifiable by lifestyle changes and reducing the total heart disease burden attributable to these factors would have a tremendous impact on public heath in general without the need for expensive medications or procedures. The challenge is to translate this knowledge into effective prevention strategies. ■

CME/CNE Instructions

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5. Once the evaluation is received, a credit letter will be sent to you. ■

CME Questions

7. Sudden death post MI is more likely to occur:
a. within the first 40 days.
b. within 40 to 90 days.
c. within 90 days to 2 years.
d. after 2 years.

8. Cardiac rehabilitation after PCI was associated with reduced:
a. myocardial infarction.
b. repeat revascularization.
c. cardiovascular mortality.
d. all-cause mortality.

9. A new meta-analysis shows that aspirin for primary prevention reduces the risk of:
a. stroke.
b. myocardial infarction.
c. cardiovascular mortality.
d. all-cause mortality.

10. Which of these four risk factors was least useful for predicting sudden death in asymptomatic women with no known vascular disease?
a. Diet
b. Exercise
c. Smoking
d. Obesity

11. True systolic BP is best estimated by:
a. two carefully done clinic measurements at one visit.
b. one research clinic measurement.
c. four to six home BP measurements.
d. two BP measurements at two different visits.

12. Compared to surgical replacement at 1 year, trans-catheter aortic valve replacement resulted in:
a. reduced mortality.
b. reduced stroke.
c. more paravalvular leaks.
d. more major bleeding.

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, Travel Medicine Advisor.*

FDA issues Multiple Drug Warnings

In this issue: FDA issues multiple drug safety alerts; ARBs and cancer risk; and FDA actions.

Avoid high-dose simvastatin

The FDA is advising physicians to avoid high-dose simvastatin (Zocor) because of the risk of myopathy and rhabdomyolysis. The agency is advising that patients should not be started on the 80 mg dose and patients who already are on 80 mg should be continued only if they have been on that dose for 1 year or longer. The recommendations are based on results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocystine (SEARCH) trial — a 7-year randomized, controlled trial comparing the efficacy and safety of simvastatin 80 mg vs simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction. There was no significant difference in the incidence of major vascular events between the two doses; however, 52 patients (0.9%) in the 80-mg group developed myopathy vs one patient (0.02%) in the 20-mg group. Of the high-dose group, 22 patients (0.4%) developed rhabdomyolysis vs no patients in the 20-mg group. The risk for myopathy and rhabdomyolysis with simvastatin 80 mg was highest in the first 12 months of treatment. Of concern, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, particularly diltiazem. The majority of patients who developed myopathy also had a genetic variant that affects coding of the transporter responsible for simvastatin uptake in the liver, resulting in higher serum simvastatin levels. The FDA not only recommends against using simvastatin 80 mg, but also suggests that the drug is contraindicated for use in patients taking itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. The maximum dose of simvastatin should be only 10 mg in patients taking amiodarone, verapamil, and diltiazem while the maximum dose is 20 mg in patients taking amlodipine and ranolazine. The new guidance recommends using a different statin if the patient's LDL targets aren't met with the 40-mg simvastatin dose. The loss of high-dose simvastatin comes as a blow to cost-concious consumers who now likely will be prescribed brand name atorvastatin (Lipitor) or rosuvastatin (Crestor). Generic atorvastatin is likely to be available in late 2011. ■

Increased risk of prostate cancer

The FDA has issued a somewhat controversial warning regarding an increased risk for high-grade prostate cancer associated with the 5-alfa reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn). Ironically, the new warning stems from studies designed to evaluate whether the drugs offer protection *against* prostate cancer. Both drugs are marketed to treat benign prostate hypertrophy and both are known to significantly decrease the prostate-specific antigen levels. In separate studies, both drugs were investigated to see if they reduce the incidence of prostate cancer. FDA experts reviewed the results of the Prostate Cancer Prevention Trial (PCPT), which evalu-

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ated finasteride vs placebo for 7 years, and the Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), which compared dutasteride to placebo for 4 years. Prostate cancers were significantly reduced in both trials; however, the reduction was limited to low-grade prostate cancers with a Gleason score of 6 or lower. The rate of cancers with a Gleason score of 8-10 was increased in both studies. Previous analyses of these data have suggested that finasteride did not increase the risk of high-grade prostate cancers, but rather made them easier to diagnose by decreasing the volume of the prostate (*Clin Cancer Res* 2009;15:4694-4699; *J Natl Cancer Inst* 2007;99:1366-1374). The FDA panel, however, disagrees and feels it prudent to add a warning to labeling of both medications regarding increased risk of high-grade prostate cancer associated with use of the drugs. The guidance further recommends that prior to initiating therapy patients should be evaluated to rule out other urologic conditions, including prostate cancer, that might mimic benign prostatic hypertrophy. ■

Actos and bladder cancer risk

The diabetes drug pioglitazone (Actos) is the subject of a new warning from the FDA regarding possible bladder cancer risk associated with use of the drug. The FDA ongoing safety review suggests that use of pioglitazone for more than 1 year may be associated with increased risk of bladder cancer based on review of a 5-year interim analysis of an ongoing 10-year epidemiologic study. Patients who had been on pioglitazone the longest and who had the highest cumulative dose of the drug had a slightly increased risk of bladder cancer. This warning falls on the heels of a French study that also showed increased risk of bladder cancer. Based on these findings, France's drug regulatory agency has suspended use of the drug. While the FDA is not recommending withdrawing the drug from the market, it does recommend avoiding pioglitazone in patients with active bladder cancer and using it with caution in patients with prior history of bladder cancer. Thiazolidinediones — including pioglitazone — have also come under scrutiny in recent years because of increased risk of congestive heart failure and bone fractures in females. ■

Chantix and cardiovascular events

The FDA has issued an alert regarding varenicline (Chantix) regarding a small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The warning regarding the smoking cessation drug was the result of review of a randomized, double-blind, placebo-controlled trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. The overall rate of adverse effects was low but cardiovascular events, including heart attack, were reported more frequently in the treatment group. The warning will result in a change in labeling for the drug and the FDA is also requiring Pfizer, the drug manufacturer, to conduct an analysis of other trials to further assess the risk. Varenicline already carries a box warning regarding neuropsychiatric symptoms including suicidality. ■

ARBs and cancer risk

Finally some good news from the FDA. After a 2010 meta-analysis showed a possible link between angiotensin receptor blockers (ARBs) and cancer, the agency has completed its own review and has found no evidence of increased risk of "cancer events" including new cancers, cancer-related deaths, breast cancer, lung cancer, or prostate cancer associated with the drugs. The agency conducted a much larger meta-analysis than the original study, including more than 150,000 patients in 31 long-term, randomized, controlled clinical trials. The rate of cancer events in the ARB group was 1.82 per 100 patient years while the rate in the non-ARB group was 1.84 per 100 patient years (relative risk of incident cancer in patients taking ARBs 0.99, 95% confidence interval, 0.92 to 1.06) There was no statistically significant difference in cancer death rates or incidence of individual cancer types. The agency continues to monitor this issue but currently states that the benefits of ARBs continue to outweigh the potential risks (summary available at FDA.gov/drugs/drugsafety/). ■

FDA actions

The FDA has approved the first generic version of levofloxacin (Levaquin). The popular fluoroquinolone is commonly used for treatment of respiratory infections, sinusitis, prostatitis, pyelonephritis and skin infections. Generic forms will include tablets, oral solutions, and injectable solutions.

The FDA has approved an abuse-resistant short-acting oxycodone tablet. Pfizer Pharmaceuticals has licensed the "AVERSION Technology" from Acura Pharmaceuticals. The technology prevents dissolving and injecting tablets by creating a gel when mixed with water or other solvents that prevents snorting crushed tablets by burning nasal passages, and also prevents intentional swallowing of excess quantities by adding niacin which causes intense flushing, itching, and sweating. Long-acting oxycodone (OxyContin) was similarly reformulated in 2010 to prevent misuse and abuse. ■

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Fracture Risk Stratification in Diabetics

Source: Schwartz AV, et al. *JAMA* 2011; 305:2184-2192.

It has recently been recognized that type 2 diabetes (DM2) increases risk for osteoporotic fracture, even though it has been demonstrated that DM2 is associated with a paradoxical increase in bone mineral density (BMD) compared to age-matched control populations. With a burgeoning prevalence of DM2 in the United States, almost 20% of the at-risk population for osteoporotic fracture has DM2, hence, clarification of risk stratification for this group is highly relevant.

The World Health Organization (WHO) and the U.S. National Osteoporosis Foundation (NOF) suggest that clinicians assess patient risk for osteoporotic fracture by means of the fracture risk algorithm (FRAX) score. FRAX, an online risk assessment tool (available free of charge at http://www.shef.ac.uk/FRAX/), allows input of patient characteristics including gender, ethnicity, body mass index, risk factors for osteoporosis, history of fracture, family history of fracture, and BMD to calculate a 10-year risk of any osteoporotic fracture as well as 10-year risk of hip fracture. Similar to the structure of the ATPIII lipid guidance, intervention is threshold-based: Anyone with a 10-year risk of hip fracture > 3%, or total fracture risk > 20%, should be considered for pharmacotherapeutics intervention.

Gathering data from three prospective observational studies (n = 9449 women, 7346 men), Schwartz et al studied the relationship between FRAX scores, BMD, and subsequent osteoporotic fractures. Of concern, for any given T-score or FRAX score, the rate of osteoporotic fractures was higher in DM2 subjects than controls. DM2 appears to be a risk factor for osteoporotic fracture, above and beyond what is predicted by BMD or FRAX. ■

Amantadine for Dysphagia in the Elderly

Source: Gokula M, et al. *Ann Long-Term Care* 2011;19:37-40.

When amantadine (AMTD) was an appropriate first-line treatment for influenza, clinicians gained familiarity with its use. In the last decade, influenza resistance to the adamantanes (i.e., AMTD, rimantadine) has essentially eliminated their utility. The safety profile of AMTD is excellent however, heightening interest in clinical use for other syndromes.

Dysphagia in the elderly can be problematic, potentially leading to feeding difficulties and aspiration pneumonia. Probably the two most common scenarios in which we encounter dysphagia are Parkinson's disease and post-stroke, each of which is associated with reduced levels of dopamine. Since AMTD is a dopamine agonist, there is putative rationale for its potential use in dysphagia.

Gokula et al report their clinical experiences with AMTD in elderly patients with dysphagia. Based on positive responses in two test cases, they performed an uncontrolled case series (n = 12) among dysphagia subjects in a long-term care facility using an AMTD dose of either 50 mg or 100 mg/d orally. By 4 weeks, 11 of the 12 subjects demonstrated better swallowing, decreased cough, and weight gain. Additionally, fewer episodes of aspiration were seen.

Because AMTD is generally well tolerated, inexpensive, and there is little other resource for addressing dysphagia, clinicians may wish to consider a clinical trial. ■

Is Homocysteine a Culprit in Aging Skin?

Source: Namazi MR, Feily A. *J Am Acad Derm* 2011;64:1175-1178.

The association of homocysteine (HCST) with atherosclerosis is as strong and consistent as cholesterol, which prompted a flurry of clinical trials in the 1990s and early 2000s attempting to improve cardiovascular outcomes by lowering HCST levels (usually with pharmacologic doses of B vitamins). Unfortunately, HCST modulation did not result in cardiovascular risk reduction, to the point that interventions aimed at HCST have been largely abandoned.

HCST might also, however, be a culprit in aging skin. Photoaging is attributed to up-regulation of cutaneous matrix metalloproteinases and down-regulation of collagen synthesis. Homocystinuria, an inborn error of metabolism characterized by marked elevation of HCST, demonstrates thin, transparent skin.

HCST negatively impacts the three primary structural elements of healthy skin: collagen, elastin, and proteoglycans. Not only does elevated HCST in-

crease degradation of these components, it also inhibits their regeneration.

There have not yet been any clinical trials to examine whether HCST reduction favorably impacts skin aging. ■

Hepatitis C Treatment by Primary Care Clinicians

Source: Arora S, et al. *N Engl J Med* 2011;364:2199-2207.

In most communities in the United States, hepatitis C (HEPc) treatment is provided by gastroenterologists. Because HEPc is now the most common cause of end-stage liver disease, and — unless trends reverse — will continue to be so for the foreseeable future, it is important that identification of HEPc infection be continued vigorously in the primary care community, since most at-risk persons see primary care clinicians as their point of initial contact with the health care system.

Treatment of HEPc offers the opportunity for cure of the disease more than 50% of the time, although persons infected with HEPc genotype I have a somewhat lower success rate. Ideally, treatment would be offered to as many infected persons as possible, yet limitations in specialist consultants who traditionally administer the treatment are an obstacle to access for some patients.

The ECHO program (Extension for Community Healthcare Outcomes) is intended to enhance opportunities for provision of health care to underserved populations through, for instance, videoconferencing technology that allows primary care clinicians to receive case-based education with specialist colleagues. Since 2003, ECHO has resulted in 800 HEPc patients being treated by primary care clinicians. The primary outcome of this ECHO-based trial was sustained virologic response, which is defined as undetectable HEPc RNA 6 months beyond the end of treatment. Encouragingly, analysis of outcomes for patients treated on-site at the University of New Mexico HEPc clinic were essentially identical with those of patients treated at distant sites by clinicians guided though case-based video conferencing. Hopefully, enlarging the spectrum of clinicians who can provide state-of-the-art care for HEPc patients will become a goal for other sites that have the capacity for video conferencing. ■

COPD Exacerbations: The EXACT Tool

Source: Jones PW, et al. *Chest* 2011;139: 1388-1394.

The impact and consequences of chronic obstructive pulmonary disease exacerbations (COPD-e) are underappreciated. This year, COPD has risen in prominence from the fourth most common cause of death to the third. COPD-e are problematic on multiple levels: as many as 10% of patients admitted for COPD-3 die in the hospital, and the mortality within the year of hospitalization is as much as 20%. Additionally, each COPD-e is associated with a further decline in FEV1 that is not restored once the exacerbation is resolved.

Jones et al have performed the first published formal analysis of COPD-e to derive an instrument known as EXACT (Exacerbations of Chronic Pulmonary Disease Tool).

Based on interviews with COPD patients (n = 410), the authors quantified items pertaining to dyspnea, cough, sputum production, chest discomfort, limitations of activity, fatigue, sleep disturbance, and anxiety associated with COPD symptoms.

Ultimately, 14 items were discerned that quantified COPD-e presence and severity. Hopefully, such a tool could be used in daily diaries of COPD patients to help identify exacerbations at the earliest possible stage so that abortive therapy could be instituted without delay. It remains to be determined whether enhanced early detection and intervention for COPD-e will favorably affect symptomatic control, hospitalizations, or mortality. ■

Are Diabetes Prevention Treatments Truly Disease Modifying?

Source: The DREAM Trial Investigators *Diabetes Care* 2011;34:1265-1269.

Prevention of type 2 diabetes (DM2) is possible by means of several different paths including diet, exercise, metformin, thiazolidinediones, orlistat, acarbose, and valsartan. Although reduced conversion from pre-diabetes to DM2 by as much as 60% has been seen in some DM2 prevention trials, critics point out that it is unclear whether any of the natural history of DM2 — that is, progressive decline in beta cell function — is impacted by currently available interventions. Animal studies have found incretin effects, such as beta cell proliferation and improved beta cell mass, but no persistence of such effects has been confirmed in humans, and most data suggest that none of these favorable effects persist once pharmacotherapy is discontinued. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Trial Investigators published an analysis of glycemic control 2-3 months after cessation of ramipril or rosiglitazone, the agents used in the DREAM trial.

Although the Heart Outcomes Prevention Evaluation trial supported a role for DM2 prevention by ramipril, this was not confirmed in the DREAM Trial, nor was there any beneficial "legacy effect." Although rosiglitazone was effective in DM2 prevention, once stopped, progression to DM2 was similar to placebo. Hence, although prevention of DM2 is achievable with thiazolidinediones, they do not appear to make a sustained impact upon underlying disease pathophysiology since drug cessation is followed by a resumption of declining beta-cell function similar to placebo. ■

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