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INSIDE

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Antithrombotic Therapy for Nonvalvular Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Source: Hart RG, et al. *Ann Intern Med* 2007;146:857-867.

In this paper, Hart, Pearce and Aguilar report the results of a meta-analysis of antithrombotic therapy in patients with nonvalvular atrial fibrillation (NVAF). The authors identified and included in their database 29 randomized trials that tested various forms of antithrombotic therapy in patients with NVAF. The trials included in the meta-analysis had a total follow-up exposure of 42,450 patient years. The patients had an average age of 71 years and a male to female ratio of 65:35. Results were reported for adjusted dose warfarin compared to placebo or no therapy, antiplatelet therapy compared with placebo or no therapy, and adjusted dose warfarin compared with antiplatelet therapy.

There were 6 randomized trials that compared adjusted dose warfarin to placebo or no therapy. These trials included 2,900 participants who had 186 strokes during a mean follow-up of 1.6 years per participant. Adjusted dose warfarin was associated with a 64% reduction in stroke with similar reductions seen for both disabling and nondisabling strokes. The absolute risk reduction in all strokes was 2.7% per year in the 8 primary prevention trials and 8.4% per year in a single secondary prevention trial. When only ischemic strokes were considered, there was a 67% relative risk reduction associated with adjusted dose warfarin.

There were 8 trials that compared antiplatelet therapy with placebo. These trials involved 4,876 participants who had 488 strokes. When aspirin alone was compared to placebo or no treatment, aspirin was associated with a 19% reduced incidence of stroke. The absolute risk reduction was 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention trials. There were 9 randomized trials that compared warfarin with various doses of

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aspirin, 3 other trials in which warfarin was compared with other antiplatelet agents and 2 trials where adjusted dose warfarin was compared to low fixed and ineffective doses of warfarin plus aspirin. When adjusted warfarin was compared with antiplatelet therapy alone, warfarin was associated with a 37% reduction in strokes. Among all patients, there was a 52% reduction in ischemic stroke.

The authors also examined several randomized trials that compared adjusted dose warfarin to other antithrombotic agents. There were 3 randomized trials in NVAF involving ximelagatran. There was an 8% reduction in stroke risk with ximelagatran compared to adjusted dose warfarin. Although 19 trials with other agents have been reported, the authors considered that the available data were insufficient for analysis.

The authors also examined major extracranial and intracranial bleeding events and total mortality. Even with the meta-analysis of this size, the frequency of these events is lower than that for ischemic strokes, so that the estimates of the effects of antithrombotic therapies are less precise. Two conclusions were, however, reached. The risk for intracranial hemorrhage was doubled with adjusted dose warfarin but the absolute risk increase was small (0.2% per patient per year) and all cause mortality was substantially reduced by adjusted dose warfarin vs placebo.

The authors conclude that in patients with NVAF, warfarin reduces stroke by approximately 60% and death by 25% compared with no antithrombotic therapy. Antiplatelet therapy reduces stroke by approximately 20%. The data support the current guideline recommendations.

COMMENTARY

This meta-analysis of a large number of studies involving antithrombotic therapy in patients with nonvalvular atrial fibrillation provides a useful resource for physicians making decisions about anticoagulation in patients with NVAF. The data clearly show that warfarin should be the gold standard against which new therapies are compared, but also indicate that alternative therapies may be appropriate in patients with few or no risk factors for stroke. The problems and complications for warfarin therapy are well summarized. Unfortunately, it appears that the bleeding complications, the major complication associated with warfarin therapy, are strongly related to the intensity of antithrombotic therapy, and safer yet equally effective alternatives to warfarin have not yet been identified.

In 2006, the guidelines for anticoagulation in patients with nonvalvular atrial fibrillation were revised. They recommend oral anticoagulation for all patients with atrial fibrillation unless there are contraindications or the patient is under age 60 without any heart disease or risk factors for atrial fibrillation (lone atrial fibrillation). For the latter patients the benefits of aspirin vs the risk of bleeding has not been established. The results of this meta-analysis can be used as a reference for the recommendations made in these guidelines.

ARBs and Diastolic Function

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Solomon SD, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomized trial. *Lancet* 2007;369:2079-2087.

LEFT VENTRICULAR (LV) DIASTOLIC DYSFUNCTION is believed to be an important mechanism of heart failure in patients with hypertension. However, there are currently no specific treatments for diastolic dysfunction. Thus, the results of the Valsartan in Diastolic Dysfunction (VALIDD) trial are of interest. In VALIDD, 482 patients with mild-to-moderate hypertension, who had no recent heart failure and were not on

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renin angiotensin aldosterone system (RAAS) inhibitors were screened by echocardiography. Those with LV ejection fraction < 50% were excluded. Diastolic dysfunction was defined as a tissue Doppler lateral mitral annular early relaxation velocity (E') lower than age specific cut-off values: < 10 cm/s for age 45-54 years, < 9 cm/s for age 55-65 and < 8 cm/s for > 65 years. The final population of 384 patients was randomized to valsartan 160 to 320 mg/day or matched placebo, plus standard antihypertensive therapy (no RAAS inhibitors) to achieve blood pressures < 135/80. The primary endpoint was the change in relaxation velocity from baseline to 38 weeks of therapy on an intention to the treat basis.

Results: E' was lower in these hypertensive patients (7.5 cm/s) as compared to historic controls (> 8 cm/s) and declined with increasing age. LV hypertrophy was present in < 3% of the randomized patients. Of the 384 patients randomized, 341 completed the study (89%). Only 10 withdrew for adverse effects and 2 left because of uncontrolled hypertension. The other 31 withdrew for a variety of personal reasons. At the end of 38 weeks, systolic blood pressure fell 13 mmHg in the valsartan group and 10 in the placebo group (P = NS) and diastolic 7 and 6 mmHg, respectively. E' increased 0.60 cm/s in the valsartan group and 0.44 in the placebo group (P = NS). However, this change from baseline was statistically significant ($P < 0.0001$). Other echo Doppler parameters also improved on therapy: isovolumic relaxation time, LV mass, left atrial volume, LV volumes and ejection fraction. However, only the improvement in isovolumic relation time was significantly greater on valsartan (-6 ms vs -2 ms, $P = 0.03$). No pre-specified subgroup did better with regard to the primary endpoint on valsartan. There were no treatment related severe adverse events and no one developed heart failure, myocardial infarction or hyperkalemia. The authors concluded that lowering blood pressure improves diastolic function regardless whether RAAS inhibitors are used.

COMMENTARY

Since experimental studies have shown greater reduction in LV hypertrophy and fibrosis with RAAS inhibitors compared to other antihypertensive agents, it was reasonable to hypothesize that valsartan may have beneficial effects on diastolic function beyond those seen with blood pressure lowering alone. This study failed to support this hypothesis, at least in terms of the primary endpoint of E' (early diastolic tissue velocity). There were some secondary endpoints that were improved more on valsartan such as isovolumic relaxation time, but valsartan did lower blood pressure slightly more than placebo plus other therapy ($P = 0.10$), so all the effects seen were probably just due to blood pressure lowering per se. So is this hypothesis dead? Probably not since this was a study of relatively young (mean age 60), obese (BMI 31) individuals with mild hypertension (systolic blood pressure 144, diastolic 86) on therapy at baseline. In addition, the duration of therapy was short (38 weeks). Also, even though 80% of these subjects had diastolic dysfunction, few had LV hypertrophy. Thus, a group with higher pressures and more LV hypertrophy may have done better on a RAAS inhibitor.

The good news from this study is that effective blood pressure lowering by any means improves diastolic function, reduces LV mass and volume, and improves systolic function. All these changes were small, but statistically significant. Whether these small changes are clinically significant and will lead to better outcomes was not tested in this study. However, it is attractive to predict that reducing blood pressure and improving diastolic function will lead to less heart failure.

Although early diastolic lateral mitral annulus Doppler tissue velocity (E') is a robust measure of diastolic function, which is less influenced by loading conditions, it is not perfect. Most echocardiography laboratories evaluate several parameters and then factor in confounders such as age, heart rhythm, mitral regurgitation, etc., before deciding what the diastolic function of a given left ventricle is likely to be. Many of these parameters were assessed as secondary endpoints in this study and their results were consistent with the observed changes in E', but noticeably absent were estimates of LV filling pressure based upon pulmonary vein flow. Also, the small changes observed in E' could have been due to the changes observed in left ventricular systolic pressure, volume and performance. Thus, this study is supportive of a beneficial role of RAAS inhibitors in diastolic dysfunction due to hypertension, but the mechanism could just be their efficacy at lowering blood pressure.

Pericarditis Triage

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Imazio M, et al. Indicators of Poor Prognosis of Acute Pericarditis. *Circulation* 2007:115:2739-2744.

Most cases of acute pericarditis are due to idiopathic or viral causes and have a benign prog-

nosis with symptomatic treatment. How to identify those cases due to specifically treatable causes or those who are not going to do well would be useful to know. Thus, this group from Torino, Italy, studied 453 patients who met criteria for acute pericarditis in the absence of acute myocardial infarction. Patients were included if they met 2 of the following criteria for acute pericarditis: typical pericarditis chest pain; pericardial friction rub; diffuse ST elevation or PR depression on ECG, and new or worsening pericardial fluid on echocardiogram. Myopericarditis was diagnosed if one of the following were present: elevated cardiac enzymes and new focal or diffuse left ventricular dysfunction by echocardiogram. All patients had coronary artery disease excluded by stress nuclear perfusion scintigraphy or coronary angiography. Pericardial tamponade was diagnosed using a combination of clinical and supportive echocardiographic signs. Clinical features in the literature associated with a poor prognosis or specific diagnoses were assessed for their predictive ability. Patients were prospectively enrolled from 1996 to 2004.

Results: A specific cause was discovered in 17% of the patients. Corticosteroid treatment was employed initially in about 25%. Multivariate analysis identified women (RR 1.67); fever (3.56), subacute course (3.97), large effusion or tamponade (2.15) and NSAID failure (2.5) as predictors of a specific cause. Elevated troponin predicted a lower risk of a specific cause (0.37). After a mean follow-up of 31 months, 21% of patients had a complication: recurrence in 18%, tamponade 3% and constriction 1.5%. Patients with a specific cause had a higher rate of complications (38 vs 18%, $P < 0.001$). Multivariate analysis showed that women (RR 1.65), large effusion or tamponade (2.51) and NSAID failure (5.50) were predictive of complications. Corticosteroid use was associated with more complications in idiopathic or viral pericarditis (48 vs 14%, $P < 0.001$). The authors concluded that fever, sub acute course, large effusions or tamponade and NSAID failure may help predict those more likely to have a specific cause of acute pericarditis or those more likely to suffer a complication.

COMMENTARY

This is a potentially clinically useful study, since currently in the developed world acute pericarditis is usually admitted to the hospital. Deployment of this risk stratification scheme could result in sending home the 80% of patients who have a viral or idiopathic etiology who are highly likely to do well. The predictors include laboratory tests and echocardiography, which would have to be readily available in the acute care setting. Let's look at the multivariate predictors identified. Female sex is not very useful as it means admitting roughly half the patients. Also, the risk ratio is < 2.0 for this variable, which is not a strong predictor. All of the other predictors have risk ratios > 2.0 . Two of the predictors identified predict specific causes and a higher risk of complications, so they would be the most valuable clinically (large effusion or tamponade and NSAID failure). Others are associated with a specific cause only: fever and subacute course. Elevated troponin was associated with lack of a specific cause.

Translating this into practice if a patient with acute pericarditis has a large effusion or tamponade, they should be admitted because these features predict complications and a specific cause. NSAID failure should also be admitted for the same reason, but this is likely to be an unusual presentation. Febrile patients or those with an indolent course likely have a specific cause that could be evaluated as an outpatient in some settings. An elevated troponin and a lack of other high-risk features would reinforce the decision to send the patient home, as long as acute myocardial infarction is excluded. Remember, the most common cause of acute pericarditis in a middle-aged man is acute infarction. These patients were excluded from this study. If you are on the fence about what to do, female sex could be used to tip the balance toward admission.

This study confirms the impression that about 80% of non-infarction-related acute pericarditis is idiopathic or viral, so most patients should not need hospitalization. Based upon their data, the most common specific causes of acute pericarditis are autoimmune disease, neoplasm and tuberculosis with or without HIV. Other bacterial causes are rare (< 1%). This may be different in less developed countries. The study also suggests the notion that steroids should not be the initial therapy of idiopathic/viral pericarditis as they increase the likelihood of recurrences. Finally, some clinical features such as warfarin use, trauma and immunosuppressed state were too infrequent to make clear judgment about their risk prediction potential. ■

Survival After Defibrillator Implantation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Lee DS, et al. Effect of cardiac and noncardiac conditions on survival after defibrillator implantation. *J Am Coll Cardiol* 2007;49:2408-2415.

Lee and co-workers examined the effects of associated cardiac and noncardiac conditions on survival in ICD recipients. The authors used the Canadian Institute for Health Information discharge abstract and same-day surgery databases and the Province of Ontario's Vital Status database and identified all patients between age 18 and 105 who received a first ICD implant between April, 1997 and March, 2003 in the province. Comorbidities present before ICD insertion were identified from the secondary diagnosis fields of the database and were classified using the Deyo-Charlson comorbidity classification system. Secondary diagnosis data were collected both during the ICD implant admission and from data for hospital admissions in the 3 years before the ICD implant. A cohort of control subjects were matched according to age, prior history of arrhythmia, prior heart failure history and number of significant noncardiac comorbidities.

There were 2,467 patients who received a first ICD implant during the study. The mean age was 62.5 + 13 years and 79% were men. Most of the patients received the ICD for secondary prevention with 82.6% having a history of ventricular tachycardia, ventricular fibrillation or cardiac arrest. Ischemic heart disease was the primary cardiac diagnosis in 59% and 42.5% had a history of congestive heart failure. The most common comorbidities were diabetes (18.2%), diabetes with microvascular complications (2.9%), chronic obstructive pulmonary disease (10.4%), cerebrovascular disease (6.4%), peripheral vascular disease (5.8%), and renal disease (5.8%). By multivariate analysis, age but not gender, was associated with an increased hazard ratio for mortality. Compared to those subjects less than 65 years of age, the hazard ratio (HR) for the age group 65 to 74 was 2.05 and for the group greater than 75, the HR was 3.0. Comorbidities were predictive of an adverse outcome. Heart failure (HR=2.33), diabetes with microvascular complications (HR=2.33), rheumatologic disease (HR=1.89), peripheral vascular disease (HR=1.50), chronic pulmonary disease (HR=1.35), and cancer (HR=1.81) were the comorbidities independently associated with mortality that were in the multivariate analysis. Prior heart failure and, in particular, heart failure with a hospital admission within the 6 months preceding ICD analysis, was also strongly associated with increased mortality. When the hazard ratio for death were adjusted for age, gender and heart failure, noncardiac comorbidities continued to be associated with increased mortality. The hazard ratios for patients with 1, 2, and greater than or equal to 3 noncardiac comorbidities were 1.72, 2.79, and 2.98 respectively. Of note, arrhythmia history was not strongly predictive of an adverse outcome. However, in the subgroup of patients with prior ventricular tachycardia, the ICD implant was associated with a significant increase in survival with an adjusted hazard ratio of 0.80.

The authors conclude that the presence of noncardiac comorbidities and prior clinical heart failure are significant predictors of death in ICD recipients. Increased age and associated comorbidities interact to lead to higher mortalities in older and sicker groups. The authors urge further research to better characterize the role of heart failure and other comorbidities as determinants of outcome in ICD recipients.

COMMENTARY

This is an important paper that reports outcomes after ICD implant in "a real world" setting. Published indications for ICD insertion are largely based on the entry criteria for the randomized clinical trials that have shown benefits with ICD use for both primary prevention of sudden death and secondary treatment of patients with sustained arrhythmias. Although these randomized clinical trials often excluded patients with significant comorbidities and investigator bias during screening eliminated many patients with complicated conditions during the screening phase, these factors are not mentioned in published indications. In this paper, we see that comorbidities, both cardiac and noncardiac, strongly influence outcome after ICD, and the data emphasize a need to interpret the published indications in light of the individual patient's overall medical condition.

Other studies have reported findings supporting the current analysis but interpretation of the data may be complex. In a prior report from the Canadian Implantable Defibrillator study, Sheldon et al reported that sicker patients were more likely to benefit (*Circulation* 2000; 101:1660-1664). Other studies have shown that patients with lower ejection fractions were more likely to receive appropriate ICD therapy. However, ICD shocks are also a predictor of mortality and in some comorbidity subgroups in clinical trials (e.g., patients with significant renal disease), no benefits from ICD therapy have been described.

These observations present an interesting problem for clinicians. Sicker patients are indeed more likely to receive ICD shocks than healthier patients, but the individual survival benefit in the sickest patients is likely to be small. Healthier patients with fewer comorbidities are less likely to receive shocks, but the survival benefit in the individual patient who does receive a shock is likely to be great. Enrolling sick patients helps a clinical trial achieve a desired number of events quickly, but societal benefit may be greater per implant if less sick patients

receive the device.

The data in this report were from ICD implants between 1997 and 2003. Most of the implants in this series were for secondary prevention. Currently, most ICD implants are for primary prevention with most primary prevention ICDs implanted in patients with very low ejection fractions or advanced heart failure. As shown here, heart failure is a major predictor of mortality. It is, therefore, likely that comorbidities would play an even more important role in the typical patient receiving an ICD today. This only makes it more important for physicians to consider the overall health status of the patient when making a decision about ICD implantation. ■

Estrogen Therapy and Early Atherosclerosis

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Manson JE, et al. Estrogen Therapy and Coronary-Artery Calcification. *N Engl J Med* 2007;356;2591-2602.

DESPITE ENCOURAGING ANIMAL STUDIES AND human observational studies such as the Nurses Health Study, prospective randomized placebo-controlled trials such as the Women's Health Initiative (WHI) failed to show that postmenopausal estrogen therapy in women who had undergone hysterectomy prevented death or myocardial infarction (RR = 0.95, CI = 0.79-1.16). However, subgroup analyses suggested that younger women may benefit (age 50-59, RR = 0.63, 0.36-1.08) as compared to older women (age 60-69, RR = 0.94; age 70-79, RR = 1.11). Thus, Manson and colleagues initiated an ancillary sub-study of WHI where CT coronary calcium scores were done in 1064 available women in the 50-59 years group after a mean of 7.4 years of treatment with equine estrogen (0.625 mg/day) or placebo. The CT scans were read at a central lab without knowledge of the women's treatment status.

Results: The mean calcium score was 83 in the estrogen group and 123 in the placebo group (P = 0.02) on an intention-to-treat analysis. After adjustment for confounders such as age and coronary risk factors, the difference was still significant (P = 0.03). When adjusted for actual treatment received, the difference was more significant (P = 0.002). The odds ratio of a calcium score > 300 in women 80% adherent to assigned treatment was 0.39 (P = 0.004). The authors concluded that in women < age 60 at initiation, estrogen therapy decreased calcified plaque burden in the coronary arteries as compared to placebo.

■ COMMENTARY

This is why Americans have lost faith in science — one day we say one thing, the next we say the opposite. It might be alright if these results were published in scientific journals and only after years of confirmatory studies were carefully analyzed and then explained to the public by the surgeon general. Instead, every brick in the wall is hyped by a hungry news media into a major study that panics everyone who is on the treatment in question or might be. Rarely after a few years is the whole wall looked at because this isn't often exciting news or there is no wall to see. Coffee is a good example; first it's bad then it's good and back and forth *ad nauseum*, so now no one pays any attention to coffee health studies. So as physicians, what do we do with these results? As it turns out, nothing.

There was never any serious attempt to start 70-year-old women on estrogens just to prevent heart disease. Estrogens were mainly used in perimenopausal women to relieve symptoms and this use was never prohibited by prior studies, we were just admonished to use the lowest doses for the shortest duration possible. Not rocket science considering the potential downsides of estrogen. Now we can prescribe for symptoms without the guilt that we are causing myocardial infarctions, and that we may be doing some good in certain women at risk for coronary heart disease. Until prospective outcome studies are done in these younger women, we still shouldn't prescribe estrogens just for cardioprotection. ■

Coronary Artery Death Rates Over the Last 20 Years

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD
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Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Source: Ford ES, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007;356:2388-2398.

CORONARY DEATHS IN THE UNITED STATES HAVE dramatically declined since 1968. A new report consists of an analysis of mortality trends for coro-

nary heart disease (CHD) mortality in the United States between 1980 and 2000, among U.S. adults 25 to 84 years of age. The document is a multi-authored analysis (United States and United Kingdom) that assesses the reasons behind the major decline in U.S. deaths from CHD during this 20 year period. The authors conclude that approximately half of the reduction in deaths is related to large decreases in the prevalence of major coronary risk factors over these 2 decades, while the other half is directly related to evidence based medical therapies. Extensive data sources are utilized, particularly the Impact Mortality Model, which incorporates major population risk factors for CHD as well as appropriate medical and surgical treatments. Data regarding the number of deaths in the United States were obtained from the U.S. Census Bureau. The analysis calculated the number of deaths from CHD that would have been expected in the year 2000 if CHD mortality rates remained unchanged since 1980. Thus, "The prevalence of the cases of CHD by diagnosis, the estimated frequency of use of specific treatments, the case fatality rate by diagnosis and the risk reduction due to the treatment, all stratified by age and sex, were obtained by public sources." Assessment of the number of deaths prevented or postponed as a result of multiple interventions was calculated. Extensive tables assess CHD clinical categories and their treatment, with estimates of the degree of deaths prevented or postponed by preventive approaches and/or specific therapies. Estimates of death reduction (total deaths as well as minimum and maximum estimates) were calculated. For example, the best estimate for aspirin reducing MI death was 2.3%; beta blockers 0.3%; ACE inhibitors 0.1%; and primary angioplasty 0.2%, for patients with acute myocardial infarction. For "secondary prevention after myocardial infarction," the same treatments were estimated to decrease death rates in year 2000 as follows: aspirin 1.5%; beta blockers 2.0%; ACE inhibitors 1.5%; statins (not available in the 1980 analysis) 1.4%. For chronic angina, the best estimate for deaths prevented or postponed related to CABG is 4.2%; statin therapy 0.3%, aspirin 0.3%. Angioplasty for chronic angina was estimated to reduce or prevent deaths by 1.3%. Tables in the manuscript present a large number of such estimates derived from the number of eligible, patients who received treatment, and were assessed for case fatality rates and absolute risk reduction. Conditions specifically explored in the overall assessment include acute myocardial infarction, unstable angina, secondary prevention after MI, chronic angina, heart failure, and hypertension.

The conclusion of this extensive analysis is that approximately half of the reduction or postponement of mortality over the 20-year period arose from medical and surgical treatments (46.6%). Favorable changes in risk factors were estimated to decrease or postpone mortality by 44%; total cholesterol reduction was robust, with a best estimate at 24%, and reduction of blood pressure at 20%. However, adverse outcomes were noted for increased BMI and diabetes, each of which resulted in an approximate 8%-10% increase in deaths.

Data from other countries, particularly New Zealand, Netherlands, the United Kingdom, are mostly comparable, with treatment responsible for approximately 35%-46% of mortality improvement and risk factors improvement responsible for approximately 44%-60%. The authors note that "the burden of CHD remains enormous, even though associated mortality rates fell by more than 40% between 1980 and 2000." They do not discuss specific advances in medical technology or pharmaceutical therapy, nor public health efforts to reduce the impact of major CHD risk factors. The concordance of this analysis with those from other countries is reassuring that the data are robust. Preventive oriented physicians and healthcare workers should take note of the major contributions of medical therapy from secondary prevention such as treatment of acute coronary syndromes and heart failure. Revascularization(CABG or PCI) in stable and unstable disease accounted for approximately 7% of the overall decline in deaths, consistent with other data. The authors underscore data showing an increase in CHD deaths in individuals with high body mass index as well as those with diabetes. An elevated BMI was calculated with a best estimate of 7.6% for an increase in deaths, and diabetes for a 9.8% increase in mortality. The authors conclude that "Future strategies for preventing and treating CHD should therefore be comprehensive, maximizing the coverage of effective treatments and actively promoting population-based prevention by reducing risk factors."

COMMENTARY

This study, although complex to report, is clearly good news. The fact that CHD mortality has decreased substantially over the 20-year period is certainly reassuring. As the population ages, and more individuals are alive who are in their 80s and 90s, the overall number of deaths may not decline proportionate to the analysis by the authors of the study, as the methodology used does not take into account the total number of deaths projected for older

groups. Figure 1 of the manuscript looks at the number of deaths prevented or postponed according to age group and gender; in the 75-84 years of age population, there is a very large portion of the population with prevented or postponed deaths, indicating that preventive measures and risk factor reductions have had a major impact in the older population, a fact not emphasized in the manuscript. This report needs to be discussed by health professionals and made available to the general population. There is clear cut, unequivocal evidence that risk factor reductions, i.e., treatment of hypertension, hypercholesterolemia, etc, pays off in terms of deaths postponed or prevented. In addition, all of our therapies, both pharmacologic and interventional, have clearly changed outlook in a favorable direction for individuals with coronary heart disease. This report indicates that we are on the right track. One should assume that the better we emphasize prevention, the better we control risk factors. The better we use evidence-based approaches, both pharmacologic and invasive, the better the likelihood that the next analysis of 20-year mortality reduction will be even more positive. ■

CME Questions

47. Perimenopausal estrogen use in symptomatic women < 60
A. increases the risk of myocardial infarction
B. reduces the magnitude of coronary calcium scores
C. increases the risk of cardiac death
D. reduces the risk of stroke

48. RAAS inhibitors improve diastolic function in hypertensives by reducing
A. the tissue effects of angiotensin
B. inflammation
C. blood pressure
D. thrombogenesis

49. Higher risk for a specific cause or complications of pericarditis is predicted by?
A. large effusions
B. tamponade
C. NSAID failure
D. all of the above

50. The relative contribution of primary prevention vs treatment in reducing the death rate from coronary heart disease is?
A. 10 vs 90
B. 30 vs 70
C. 50 vs 50
D. 70 vs 30

51. Stroke prevention in nonvalvular atrial fibrillation is best achieved by
A. warfarin
B. aspirin
C. dipyridamole
D. clopidogrel

52. Mortality after ICD placement is adversely affected by?
A. age
B. heart failure
C. ventricular tachycardia pre-implant
D. A and B

Answers: 47.(b) 48.(c) 49.(d) 50. (c) 51.(a) 52.(d)

CME Objectives

The objectives of Clinical Cardiology Alert are:

• To present the latest information regarding diagnosis and treatment of cardiac disease;

• To discuss the pros and cons of these interventions, as well as possible complications;

• To discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To present the current data regarding outpatient care of cardiac patients. ■

PHARMACOLOGY WATCH

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

SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■