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INSIDE

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Lifetime Follow-up Care after Childhood Cancer

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

Dr. Ferris reports no financial relationship to this field of study.

Synopsis: *Lifetime surveillance is required after successful treatment of childhood cancers, since up to 75% of survivors develop serious complications and other late effects.*

Source: Haddy RI, Haddy TB. Lifetime follow-up care after childhood cancer. *J Am Board Fam Med* 2010;23:647-654.

Decreasing death rates from childhood cancers leave large numbers of adults as survivors needing monitoring for both cancer recurrence and late effects of treatment. Childhood cancers are diverse and less often are solid cancers compared to adults; present cure rates are > 80%. Most common are leukemias, brain and nervous system tumors (both malignant and non-malignant), and lymphomas. Nephroblastoma, which requires removal of the affected kidney, is the second most successfully managed malignancy of childhood; the highest cure rate is for Hodgkin lymphoma at 95.5%.

Treatment for most childhood cancers includes adjuvant radiation and chemotherapy. Since their tissues are still growing and developing, children and adolescents are especially sensitive to radiation and chemotherapy damage. For Hodgkin's lymphoma where the mantle area or chest is targeted, complications can include thyroid disease, lung and breast cancers, and pulmonary complications. Radiation to the brain can induce serious neurocognitive late effects.

Bone marrow transplantation is increasingly used and is associated with major transplant toxicities: graft rejections, graft-versus-host disease, and sequelae of prolonged immunosuppression, such as infections and septicemia. Splenectomy was utilized in the past as

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part of the Hodgkin's staging procedures; these patients must have early evaluation and treatment of febrile illnesses along with immunizations to protect against bacterial infections.

Late effects of childhood cancer treatment are reported in approximately 75% of survivors, with the majority related to treatment toxicity. Most common are delays in growth and development, including intellectual and sexual maturation. Decreased growth hormones can result from radiation damage to the hypothalamus, along with decreased FSH, LH, testosterone, and estradiol. Blood levels can be monitored, along with DEXA bone scans, since failure to reach peak bone mass may result in early osteoporosis. Infertility problems can also result secondary to radiation and chemotherapy with alkylating agents. Learning problems and hyperactivity have been attributed to cranial radiation, which in the past was used prophylactically for leukemias; cataracts and hearing loss can also result from chemotherapy toxicities.

Recurrence of cancer and second malignancies are the leading cause of death among survivors of more than 15 years. The excess risk for survivors continues for at least three decades, but second cancers are often successfully treated. Solid tumors may result from radiation effects, and myelodysplasia and acute myelocytic leukemia are seen from chemotherapy.

■ COMMENTARY

Primary care clinicians can play a vital role in the long-term survival of childhood cancer survivors. Along with the routine health care maintenance that we provide to all patients, an awareness of major treatment toxicities and developmental effects is necessary to detect and treat problems that can significantly affect quality of life. Even the normal effects of aging, such as cardiovascular disease and osteopenia, may be accelerated or worse in these survivors due to their underlying health status. Guidelines developed by the Children's Oncology Group are a good resource for comprehensive long-term follow-up and are kept updated through a website (www.survivorshipguidelines.org).[1,2]

Attention to psychological well-being is particularly important, since childhood cancer survivors are more likely to report depression and even post-traumatic stress disorders compared to the general population. There may be more physical health problems resulting in lower rates of employment and even job discrimination. The primary care clinician is in a unique position to help these survivors through both empathetic support and monitoring for complications of cancer treatment and detection of new cancers. ■

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Is It a Coincidence that Death Rhymes with Breath?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant for Cephalon, and serves on the speakers bureaus for Resmed and Respironics.

Synopsis: *Pulmonary function can help predict cardiovascular death risk in individuals in the intermediate-risk group of Framingham Risk Scores.*

Source: Lee HM, et al. Forced vital capacity paired with Framingham Risk Score for prediction of all-cause mortality. *Eur Respir J* 2010;36:1002-1006.

These authors set out to discover whether simple spirometric pulmonary function measures can improve on the prediction of all-cause mortality provided by Framingham Risk Score (FRS).[1] To do this, they undertook a secondary analysis of 5485 never-smoking American adults from the Third National Health and Nutrition Examination Survey (NHANES).[2] Participants had baseline pulmonary function measured, and follow-up data were available for a mean of about 9 years. Never-smoking status was based on self-report and cotinine levels, and cardiovascular disease was defined by self-report for stroke, congestive heart failure, and myocardial infarction.

The investigators stratified the two primary spirometric measures, the Forced Vital Capacity (FVC) and the Forced Expiratory Volume in one second (FEV1) into three categories: low (≤ 85% predicted), borderline (86%-94% predicted), and normal (≥ 95% predicted). They then applied these stratifications of low, medium, and high pulmonary function to the three Framingham Risk group classifications of 10-year cardiovascular mortality risk groups of low (< 10%), intermediate (10%-20%), and high (> 20%). The aim was to determine if pulmonary function could enhance the accuracy of cardiovascular mortality risk predicted by the Framingham Risk Score.

The low, intermediate, and high Framingham Risk Score groups included 79.5% (n = 4361), 10.1% (n = 555), and 10.4% (n = 569) of the people in this cohort, respectively. Men had a 4% greater 10-year risk of coronary heart disease estimated by the Framingham than women did. Caucasians had the highest 10-year risk of heart disease at 5.5% compared to African-Americans at 3.1% and Mexican-Americans at 3.5%. There were no significant differences in the predicted FVC across sex, but African-Americans had lowest predicted FVCs and Mexican-Americans had the highest.

Both the FVC and the FEV1 increased the accuracy of the FRS in predicting cardiac death in those who were in the intermediate FRS group; in this group, mortality was 10.7%, 18.2%, and 42.8% per 1000 person-years from highest to lowest FVC categories, respectively. Those with low FVC had an almost three-fold greater risk of death than those with normal FVC. The authors concluded that evaluation of lung function may be useful to improve risk stratification in persons with intermediate cardiovascular disease risk.

■ COMMENTARY

Heart disease remains the leading cause of death in the developed world.[1,3] The Framingham Risk Score (FRS) is a widely used tool to estimate 10-year coronary heart disease; it includes multiple risk factors such as age, sex, smoking history, systolic blood pressure, and total cholesterol and high-density lipoprotein cholesterol risk, and is generally applied to those who have not been already diagnosed with heart disease. The Framingham is an imperfect predictor, however, and efforts to tweak its accuracy are ongoing.[1] In that regard, pulmonary function testing, which is safe, simple, and inexpensive, is an ideal candidate to incorporate into the Framingham predictive model. Reduced pulmonary function predicts cardiovascular disease and death,[4-7] as well as all-cause mortality even in never-smokers.[8-10]

This application of pulmonary function to the FRS is a logical approach to improving its predictive value. This investigation has indeed demonstrated that spirometric measures can improve risk stratification for mortality, particularly for people in the intermediate Framingham group. This is not an inconsequential finding, as people in this risk group are often quite heterogenous. In their discussion, the authors note that people with low FVC in the intermediate risk group might be "bumped up" into the next-highest risk category, and might be considered for more aggressive clinical management, as has been suggested for other measures of subclinical disease.

A caveat or two is in order here. As a pulmonologist, I am used to considering all spirometric predicted values above 80% as "normal." In this study, those whose FVC or FEV1 were below 85% were classified in the "low" group. This report will change the way I think about these predicted percentiles.

As to the mechanism by which pulmonary function could influence cardiovascular disease, the authors note that inflammation is the causal pathway of both pulmonary and cardiac disease,[11,12] and is a likely culprit.

What does this mean to us as clinicians? In this era of increasing demand for high-tech, inexpensive risk assessment tools such as spiral CT scans and coronary artery calcification scores, we still have a an expensive, radiation-free, highly predictive tool: good old pulmonary function testing. ■

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Should Everyone Be on Fish Oils?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *Marine n-3 PUFAs act as pleiotropic agents on the cardiovascular system with a diverse range of effects most of which are beneficial for patients with known cardiovascular disease and possibly, they may even have beneficial effects with regard to the primary prevention of cardiovascular disease.*

Source: Saravanan P, et al. Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 2010;376:540-550.

THE MARINE OMEGA-3 POLYUNSATURATED FATTY ACIDS (N-3 PUFAs) eicosapentaenoic acid and docosahexaenoic acid are present mainly in all the fish and commercially available supplements which are available either over the counter as fish oils or as concentrated pharmaceutical preparations. Fish oil supplements have been becoming increasingly popular because several health benefits have been attributed to them in both the medical and lay literature. Substantial benefits have been reported in relation to diseases of the cardiovascular system and, in fact, published medical guidelines recommend use of these agents in some cardiac disorders.[1,2] Although much research had been focused on this area during the past three decades, such basic issues as the appropriate doses needed to achieve beneficial reduction in cardiovascular events are still unclear.

■ COMMENTARY

Numerous prospective epidemiological studies have reported that high fish consumption was associated with a lowered mortality from coronary artery heart disease,[3-6] and this hypothesis has been supported by findings of the landmark DART study,[7] which was a randomized secondary prevention trial concerned with long-term dietary intervention in men who had suffered myocardial infarctions (MI). A 30% reduction in total mortality and morbidity related to coronary artery heart disease (CAD) was reported in patients who were randomly assigned to consumption of fatty fish twice weekly. Another large intervention trial of secondary prevention after MI demonstrated a substantial reduction in all-cause and cardiovascular mortality in patients who were treated with only 1 g per day of n-3 PUFA supplementation.[8] Data on the effects of these agents on the risk of development of CAD in healthy participants are inconsistent; however, the available evidence in primary prevention of CAD suggests that those patients with hyperlipidemia and/or diabetes might benefit the most by using fish oil. The main benefit reported for secondary prevention relates to the reduction in occurrence of sudden cardiac death, especially in patients with previous MI.[9] Much research has been devoted to the antiarrhythmic affects of these agents and it has been suggested that the conflicting findings may be attributable to differences in the mechanisms of arrhythmia initiation in subsets within the study populations. Finally, it must be noted that no significant reduction in sudden cardiac death or CD events was reported in a cohort of patients who had received optimal use of conventional therapy

such as beta blockers, statins, and angiotensin converting enzyme inhibitors and even in patients who had a high rate of revascularization procedures performed,[10] suggesting that n-3 PUFA therapy may be of no additional value in patients who already are receiving maximum medical therapy for their cardiac condition.

The risk of heart failure appears to be inversely related to fish consumption and, in an extremely large study with 60,000 participants who were followed for up to 13 years, there was a reduction in deaths attributable to heart failure in those participants who reported an increase in fish intake.[11,12] Thus far, no significant data are available regarding the effect of n-3 PUFA on the prevention or reduction of stroke in symptomatic or asymptomatic patients with or without atherosclerotic carotid arterial disease. A consistent effect of these agents is their ability to lower plasma triglyceride concentrations by reducing the hepatic synthesis of triglycerides and by increasing clearance of circulating triglycerides.[13] Because prior studies have demonstrated significant benefit in the reduction of cardiovascular events in patients with type 2 diabetes, large prospective studies assessing the role of the n-3 PUFA intake upon the reduction of the risk of cardiovascular events are underway.[14]

It has been suggested that the dietary intake of fish is the most desirable way to increase the n- 3 PUFA intake, but it must be recognized that 1 g per day of the supplement is equivalent to the fish oil present in about 55-85 g of fresh tuna, sardines, salmon, or trout and in 652 g of Atlantic cod fish. These high intakes of fish are extremely difficult to achieve in most parts of the world; therefore, an argument can be made for prescribing supplements to all patients for whom reliable increases in n-3 PUFA are indicated.[15] Finally, it should be noted that the joint American College of Cardiology and American Heart Association guidelines statement on the use of n-3 PUFA currently recommends an intake of at least two fish meals per week in patients with known CAD and supplemental therapy for 1 year with 1 g per day of n-3 PUFA for those patients who have had a prior myocardial infarction.[1] The evidence for these recommendations have been lent support by the results of many observational studies, although the recommendation for treatment of patients post myocardial infarction were derived from only one study;[8] therefore, further large scale investigations are needed in this patient group as well as in the overall area of primary prevention.

In conclusion, marine n-3 PUFAs act as pleiotropic agents on the cardiovascular system and appeared to be associated with beneficial anti-inflammatory, anti-atherosclerotic, anti-immunomodulatory, and anti-arrhythmic effects. However, assessment of the effectiveness of these agents in the setting of optimum conventional drug therapy and elucidation of the mechanisms of action of the perceived benefits needs to be established on a larger scale in carefully controlled, double-blind trials. ■

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Pharmacology Update

Dabigatran Etexilate mesylate Capsules (Pradaxa®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

THE FIRST ORAL THROMBIN INHIBITOR HAS BEEN APPROVED by the FDA for reducing the risk of stroke in patients with atrial fibrillation. Dabigatran, which is taken twice a day and does not require monitoring, may be an alternative to warfarin for many patients with atrial fibrillation. Dabigatran is marketed by Boehringer Ingelheim Pharmaceuticals as Pradaxa®.

Indications

Dabigatran is indicated for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[1]

Dosage

The recommended dose is based on the patient's creatinine clearance (CrCl). For those with CrCl > 30 mL/min, the dose is 150 mg twice daily. For those with CrCl 15-30 mL/min, the dose is 75 mg twice daily.[1]

Dabigatran is available as 75 mg and 150 mg capsules.

Potential Advantages

Compared to an adjusted-dose warfarin, dabigatran (150 mg twice daily) was associated with a lower rate of stroke and systemic embolism.[1,2] Dabigatran does not require monitoring of INR and is neither metabolized by, nor affects the activity of, the CYP 450 isoenzymes.

Potential Disadvantages

Gastrointestinal adverse events were more common with dabigatran than warfarin in clinical studies (35% vs 24%).[1] Twenty-one percent of patients discontinued participation in the clinical trial compared to 16% for warfarin. There is a higher rate of gastrointestinal bleed (1.6% vs 1%) and myocardial infarction (0.74 %/year vs 0.53%/year) with dabigatran.[2] Dabigatran does not have a specific antidote. Rifampin, a P-gp inducer, decreases the systemic exposure to dabigatran and should be avoided.

Comments

Dabigatran is an oral, selective, competitive, reversible inhibitor of human thrombin. Its efficacy in reducing the risk of stroke was shown in a 2-year study, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study.[1,2] More than 18,000 patients with atrial fibrillation were randomized to dabigatran (110 mg twice daily), dabigatran (150 mg twice daily), or adjusted-dose warfarin. The mean age was 71 years, 83.6% were men, and the mean CHAD2 score was 2.1. The primary efficacy outcome was stroke or systemic embolism and primary safety outcome was major hemorrhage. The primary net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage. Since the 110 mg dose was not approved, only the results of the 150 mg twice daily dose compared to warfarin will be discussed here.

The rate of primary outcome was superior for dabigatran (1.11 %/year compared to warfarin 1.69%/year; relative risk, 0.66; 95% confidence interval, 0.53-0.82). This difference was not evident in study sites with better INR control (median of 67% or higher). There was no difference in major bleeding (3.11%/year vs 3.36 %/year). Rate of hemorrhagic stroke was lower for dabigatran (0.10%/year vs 0.38%/year), as was intracranial bleed (0.30%/year vs 0.74%/year); mortality was numerically better for dabigatran (3.64% vs 4.13%), but did not each statistical significance ($P = 0.051$). Myocardial infarction was numerically higher with dabigatran (0.74%/year vs. 0.53%/year; $P = 0.07$). There was no significant difference in net clinical benefit outcome (6.91%/year vs 7.64%/year; $P = 0.10$). In patients with previous stroke of transient ischemic attack (n = 2428) the effect of dabi-

gatran (150 mg twice daily) was similar to warfarin in terms of the rate of stroke or systemic embolism and major bleed.[3]

Clinical Implications

Dabigatran is the first oral anticoagulant to be approved and is the first serious competitor to warfarin. Warfarin therapy requires INR monitoring as well as awareness of food and drug interactions. Dabigatran has been shown to be superior to warfarin, particularly in patients enrolled in centers with less-than-optimal INR control (median time in therapeutic range less than 67%). Potential drawbacks include a possible increase in myocardial infarction, gastrointestinal adverse events, lack of an antidote, and lack of long-term safety. The 75 mg dose was not approved based on efficacy, but rather on dose-proportional pharmacokinetics and renal clearance. Several other oral anticoagulants are in the pipeline including the factor X inhibitors, apixaban, rivaroxaban, and edoxaban. ■

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CME Questions

59. Which of the following statements about childhood cancer survivors is *true*?

a. Increased survival has resulted in the need for more monitoring.
b. Up to 75% will experience late effects of cancer treatment.
c. Increased risk of recurrent or new cancers can persist for 30 years.
d. Depression occurs at higher levels compared to non-cancer survivors.
e. All of the above

60. When combined with the Framingham Risk Score (FRS), pulmonary function testing can:

a. enhance predictive value for mortality for all FRS groups.
b. have no effect on the predictive accuracy of the FRS score.
c. improve predictive accuracy in the intermediate group only.
d. negate the predictive value of the FRS, rendering it ineffective.

61. The joint American College of Cardiology and American Heart Association statement on n-3 PUFA use in patients with coronary artery disease recommends:

a. an intake of at least two fish meals per week.
b. an intake of one fish meal per week with 1 g per day of n-3 PUFA ethyl esters.
c. supplemental therapy for 1 year of 4 g per day of n-3 PUFA ethyl esters for those who have suffered a myocardial infarction.
d. four fish meals per week for primary prevention of symptomatic coronary artery heart disease.

Answers: 59. e, 60. c, 61. a.

CME Objectives

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
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Extended-release Carvedilol + Lisinopril in Hypertension

Source: Bakris GL, et al. Effect of combining extended-release carvedilol and lisinopril in hypertension. *J Clin Hypertens* 2010;12:678-686.

Since the publication of the ALLHAT trial, clinicians have progressively relied upon diuretic-based regimens to manage hypertension (HTN). On the other hand, in the ALLHAT trial, overall mortality was similar with diuretic, calcium channel blocker, or ACE inhibitor, lending credence to the idea that any of the treatment choices is reasonable, at least for the endpoint of all-cause mortality. There was no beta blocker arm in the ALLHAT trial; instead, beta blockers were used as add-on treatment.

Ultimately, only a small minority (about 25%) of patients with HTN are able to be controlled with monotherapy. Hence, clinicians must feel comfortable taking best advantage of available combinations of treatment. The COSMOS Study (Coreg and Lisinopril Combination Therapy in Hypertensive Subjects) randomized 656 hypertensive patients to treatment with extended-release carvedilol, lisinopril (LIS), or both. Each agent, as monotherapy or in combination, was used in the full range of therapeutic doses (e.g., LIS 10 mg, 20 mg, and 40 mg).

Although perhaps counter-intuitive, it was only when the highest doses of combination therapy were compared with highest-dose monotherapy that an advantageous differential of diastolic BP lowering was seen. This is the first clinical trial to combine these specific agents, and the fact that simultaneous initiation of both medications was very well tolerated is reassuring. ■

When Should a Non-diabetic A1c Be Rechecked?

Source: Takahashi O, et al. A1c to detect diabetes in healthy adults: When should we recheck? *Diabetes Care* 2010;33:2016-2017.

Recently, the ADA has advocated the use of A1c to diagnose diabetes, indicating that we may now make a diagnosis of diabetes with an A1c ≥ 6.5. We do not have explicit guidance about the frequency with which persons whose A1c falls below the diagnostic threshold should be rechecked.

Takahashi et al followed all adults participating in preventive health check-ups (n = 16,313) at the Center for Preventive Medicine at St. Luke's International Hospital, Tokyo, from 2005 to 2008. Three years after enrollment, among those without diabetes at baseline, 3.2% had reached an A1c ≥ 6.5. However, the likelihood of progressing to diabetes varied widely and was dependent upon the baseline non-diabetic A1c: Only 0.05% of persons with an A1c < 5% became diabetic vs 20% of those with an A1c 6.0%-6.4% at baseline.

Based upon their observations, the authors suggest that if baseline A1c is < 6.0%, rescreening is unlikely to be valuable in less than 3 years. On the other hand, the high frequency of A1c progression when baseline A1c is 6.0%-6.4% merits consideration of annual re-screening. ■

Office-based Colon Cancer Screening?

Source: Nadel MR, et al. Fecal occult blood testing beliefs and practices of U.S. primary care physicians: Serious deviations from evidence-based recommendations. *J Gen Intern Med* 2010;25:833-839.

Colon cancer screening (CCS), when properly done, has been shown to improve outcomes. Unfortunately, available screening methods suffer from underutilization, misinterpretation, and inappropriate follow-up.

Nadel et al compared data obtained from the National Survey of Primary Care Physicians' Recommendations and Practices for Cancer Screening during two time intervals (1999-2000 and 2006-2007), compiling responses from PCPs (n = 1134).

Before exploring the results, it is important to note recommendations about CCS. First, in-office screening of samples obtained through digital rectal examination (DRE) is not a recommended strategy; a single, in-office fecal occult blood testing subsequent to DRE will miss 95% of advanced neoplasia. Rather, annual CCS by means of three separate stool samples collected at home is appropriate: ACS guidelines suggest annual screening by three out-of-office samples tested with high-sensitivity guaiac or FIT.

One-fourth of primary care physicians reported using a single in-office sample in 2006-2007, down from one-third in 1999-2000. Low-sensitivity guaiac utilization decreased in the same interval from 77.4% to 61.1%. ■

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