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Comparing Recommendations by Urologists and Radiation Oncologists for Treatment of Clinically Localized Prostate Cancer

ABSTRACT & COMMENTARY

Synopsis: *The survey revealed that for clinically localized disease, the majority of both groups of specialists would recommend for patients the therapy that they themselves deliver.*

Source: Fowler FJ Jr., et al. *JAMA* 2000;283:3217-3222.

According to fowler and colleagues, about 180,400 men will be diagnosed as having prostate cancer in the United States this year, most with clinically localized disease who will mainly choose one of three therapies: radical prostatectomy, external beam radiotherapy, or brachytherapy. A 1988 survey of urologists and radiation oncologists revealed that when asked what they would personally do if diagnosed as having clinically localized prostate cancer, 79% of U.S. urologists chose radical prostatectomy while 92% of radiation oncologists chose external beam radiotherapy. The purpose of this study was to again survey the two specialties to determine whether the current era of prostate-specific antigen (PSA) testing has led to an alteration in such polarity of views as well as gain further insight beyond simply preference for treatment.

When asked if primary care practitioners (PCPs) should include PSA testing as part of the routine physical examination, close to 100% of both specialists believed that screening was appropriate for patients between the ages of 50-70 years of age. Interestingly, beyond age 70 years, 43% of oncologists continued to recommend the screening test, compared to only 16% of urologists. When asked to compare radical prostatectomy and external beam radiotherapy for patients with more than 10 years life expectancy, 93% of urologists thought that radical prostatectomy was better compared to 72% of radiation oncologists' perception that the two therapies were equivalent. Interestingly, even when asked about tumors with low Gleason scores (3 or 4 and PSA no higher than 5 ng/mL), only 10-20% of either specialty favored watchful waiting, which dropped to near zero for higher grade tumors. The two groups were essentially

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identical in predicting the likelihood of aggressive therapy causing either sexual dysfunction or impotence.

The survey again revealed that for clinically localized disease, the majority of both groups of specialists would recommend the therapy for patients that they themselves deliver. A majority of radiation oncologists stated that they believed that radical prostatectomy is overused and about half thought that radiation and brachytherapy are underused. In contrast, 51% of urologists thought that radical prostectomy was used at about the correct rate and 37% thought that external beam radiation was overused. There was no uniformity of opinion by either specialty regarding the appropriate use of brachytherapy. As Gleason scores and PSA levels increase, both groups started to consider androgen deprivation as primary therapy, and urologists began to recommend radiation more often than surgery.

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COMMENT BY MICHAEL K. REES, MD, MPH

In an accompanying editorial, Wilt reminds us that—to date—there is no conclusive evidence that screening and treatment of prostate cancer improve either survival or quality of life and that the only randomized, controlled trial (RCT) comparing surgery with watchful waiting demonstrated no difference in survival up to 23 years.[1] He notes that physicians in Sweden and the United Kingdom are much less aggressive in their approach to both screening and therapy intended to be curative; nevertheless, mortality rates for prostate cancer decreased in Sweden from 1993 to 1996 and U.K. mortality rates are similar to those in the United States. While the rate at which prostate cancer is diagnosed in the United States has increased about 80 per 100,000 since the early 1990s, prostate cancer death rates have only decreased by four per 100,000 and remain greater than in the 1970s-80s. Wilt argues that this small decline began too early after widespread PSA testing and early intervention to be due to these factors.

According to Wilt, though well intended, selective interpretation of uncontrolled reports leads to advocating a particular option by a specialist or country and dismissal of other options and, in many instances, the results of well conducted RCTs disprove therapeutic recommendations that were based upon observational studies. He argues that dissemination of unsubstantiated theories as proven medical care increases practices likely to be harmful. "For example, because most prostate cancers do not cause mortality or serious morbidity, early intervention is not necessary in the vast majority of men. However, while watchful waiting appears to provide comparable survival, and avoids the harmful side effects that can occur with surgery or radiation therapy, it is rarely recommended in the United States."

Perhaps no area of decision making so perplexes and frustrates the PCP as does therapy of prostate cancer. In a time when we take pride in basing therapeutic decisions on the results of well conducted randomized, double-blinded, controlled trials, for this disease we remain largely dependent on expert opinion. However, when it comes to choosing therapy for a clinically localized tumor, urologists and radiation oncologists each strongly favor the form of therapy that they deliver—both of which are associated with a high rate of severe morbidity. They express no uniformity of opinion on the appropriateness of brachytherapy and are almost uniformly against the option of watchful waiting, unless the tumor is extremely low grade and life expectancy is less than 10 years.

I agree with Wilt that there is an urgent necessity for entering our patients with prostate cancer into RCTs.

"Accrual in RCTs is likely to increase by enhancing public awareness of the importance and benefits of clinical trials as the treatment of choice for cancer and by making participation socially, medically, and financially acceptable and preferred as the best current choice for patients and physicians." Currently, there are at least three trials that may be available to our patients, the Prostate Cancer Intervention Versus Observation Trial (PIVOT), the Prostate, Lung, Colorectal and Ovarian Screening Trail, and a trial comparing brachytherapy with surgery. For information on the availability of RCTs, see http://clinicaltrials.gov or http://cancernet.nci.nih.gov/pdg.html.

Finally, in a humorous personal view, Tannock observes that, to date, our major accomplishment has been to eradicate asymptomatic prostate cancer.[2] "Unfortunately, in medicine some discoveries may lead to more harm than good. It remains to be seen whether there will be net benefit following the discovery of PSA. In the meantime, a large population of men who, 15 years ago, would have remained happily unaware of any problem, now have impaired quality of life because they are consumed by anxiety about their PSA. Such is progress." ❖

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Cost-Effectiveness of Early Discharge After Uncomplicated Acute Myocardial Infarction

ABSTRACT & COMMENTARY

Synopsis: *A cost analysis for hospitalizing patients with uncomplicated acute myocardial infarction beyond three days after thrombolysis has an estimated cost of $105,629 per year of life saved and is economically unattractive by current standards.*

Source: Newby LK, et al. *N Engl J Med* 2000;342:749-755.

Newby and associates noted that previous investigators have suggested the feasibility and safety of discharging patients as early as three days after infarction. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-1 (GUSTO-1) study that looked at four thrombolytic treatment groups, the mortality for patients without cardiac complications had 30-day mortality rates of 1%. Since the mortality rates for uncomplicated infarctions is low, Newby et al decided to assess the cost effectiveness of discharging patients 72 hours after thrombolysis in patients with uncomplicated myocardial infarction (MI).

The study group consisted of the 41,021 patients who participated in GUSTO-1. Approximately 22,000 individuals had an uncomplicated course, defined as no mortality or serious cardiovascular events and discharge after 96 hours. Newby et al used a decision analysis to estimate the cost per year of life saved if patients with an uncomplicated course were discharged at 72 hours instead of after four days. They determined the number of treatable ventricular arrhythmias after day 3 and assumed that these patients would have died if they were discharged. The primary costs considered were the costs associated with an additional hospital day. Costs for lab testing was assumed to be similar for both the inpatient and outpatient setting. The model assumed that all inpatient deaths from arrhythmia were untreatable and that discharged patients had ready access for care of complications. Newby et al specifically noted that their analysis applied only to patients with uncomplicated thrombolysis and not to other types of patients such as those undergoing bypass graft surgery or angioplasty.

The rate of ventricular arrythmias for all GUSTO-1 participants dropped dramatically after 48 hours. After 72 hours, there were only 16 serious arrythmias among the approximately 22,000 patients with uncomplicated courses at day 3. Three of these patients died. Newby et al conclude that hospitalizing a patient with an uncomplicated course cost an average of $105,629 per year of life saved. The sensitivity analysis estimated that costs ranged from $65,777 per year of life saved to $183,524. They also note that risk stratification to identify those most at risk for an arrhythmia and keeping these individuals for 96 hours may also be a cost effective method.

COMMENT BY MARTIN LIPSKY, MD

This study showed that in the described setting, hospitalizing patients after an uncomplicated course following thrombolysis is unattractive by the conventionally accepted economic threshold of $50,000 per year of life saved. However, for those of us in primary care, it is clear that an additional day of hospitalization may offer significant benefits that were not studied. A cardiac event is a catastrophic event and an extra day in the hospital setting might have an important effect on quality of life and preparing family members to have the patient return home. In addition, an extra day might be used for

intensive education about lifestyle issues such as diet and exercise that might offer a long-term advantage over early discharge. Also, when we know that so many individuals with heart disease do not receive such widely accepted treatments as aspirin, beta-blockers, and ace inhibitors, I wonder if earlier discharges might not reduce patient adherence and having these medicines prescribed before discharge. Despite these concerns, I agree that this thoughtful analysis shows that an extra day of hospitalization may not be cost beneficial. However, I would like to see confirmation of these findings and also perhaps a risk stratification plan before making this standard treatment. ❖

Treating Hypothyroidism Isn't Always as Simple as it Seems

ABSTRACT & COMMENTARY

Synopsis: *Calcium carbonate may interfere with the absorption of levothyroxine.*

Source: Singh N, et al. *JAMA* 2000;283:2822-2825.

The effect of calcium carbohydrate on the absorption of levothyroxine is important since many postmenopausal women may be taking this combination of medications.

This study involved 20 hypothyroid patients (age range, 27-78 years; n = 11 men). All subjects had normal free T4 and thyrotropin levels before beginning the study. The subjects were instructed to take 1200 mg/d of elemental calcium carbonate along with their thyroxine for three months.

Levels of free T4, total T4, total triiodothyronine (T3), and thyrotropin were taken at baseline before taking calcium carbonate, at two and three months while taking calcium carbonate with their thyroxine, and two months after discontinuing the calcium carbonate.

Mean free T4 and total T4 levels were significantly reduced during the calcium carbonate period and increased when the calcium carbonate was discontinued. Mean free T4 levels were 1.3 ng/dL at baseline, 1.2 ng/dL during the calcium carbonate period, and 1.4 ng/dL after calcium carbonate was discontinued.

Total T4 levels followed a similar pattern. Mean thyrotropin levels increased significantly from 1.6 mL U/L at baseline to 2.7 mlU/L during the calcium carbonate period and decreased to 1.4 mL U/L after calcium discontinuation. Twenty percent of the patients had thyrotropin levels during the calcium carbonate period; the highest level was 7.8 mL/L. Mean T3 levels did not change.

The conclusion of the study was that calcium carbonate reduces T4 absorption and increases thyrotropin levels.

COMMENT BY RALPH R. HALL, MD, FACP

Singh and colleagues also note that other drugs have been shown to interfere with the absorption of levothyroxin. These include sulfate, sucralfate, bile acid sequestrants, and aluminum hydroxide. High-fiber diets have also been shown to impair thyroxine absorption. Other drugs such as phenytoin (Dilantin), carbamazepine (Tegretol), and sertraline (Zoloft) may accelerate disposal.

It would have been interesting to see if thyroid function would continue to worsen had the calcium carbonate been given over a longer period of time. The liklihood is that there would have continued to be a worsening of the status of her thyroid function.

It behooves us to monitor all patients who are taking other medications with their thyroxine a little more often. Polypharmacy is complicated. ❖

Predicting Adverse Postoperative Outcomes in Patients Aged 80 Years and Older

ABSTRACT & COMMENTARY

Synopsis: *Preoperative comorbidities were more important than intraoperative events in predicting the 25% adverse postoperative outcomes in this group of geriatric surgical patients who sustained an in-hospital mortality rate of 4.6%. Neurological and cardiovascular complications were the leading causes of morbidity. The only intraoperative event shown to be predictive of complications was the use of vasoactive agents.*

Source: Liu LL, et al. *J Am Geriatr Soc* 2000;48:405-412.

Liu and colleagues at the university of california-San Francisco reviewed medical records from all noncardiac surgical admissions at two teaching hospitals for patients aged 80 years and older over a one-year period in 1995 (identified from an operating room database). Ambulatory surgery and cardiothoracic cases were excluded; 367 patients who underwent 410 procedures were studied. Anesthesia records, type of surgery,

intraoperative drug records, and O_2 saturation were also studied. Adverse outcomes were verified by a reviewer blinded to the patient's preoperative status. Discharge disposition and length of stay were also evaluated.

Results from both hospitals were combined together when demographics and preoperative predictors were found to be similar. A total of 86% had one or more preoperative risk factors, the most common being hypertension (50%), coronary artery disease (30%), preexisting neurological disease (29%), and pulmonary disease (23%). Fully 30% had a history of smoking. Only 14% had no preoperative conditions; 41% had three or more conditions. The most common procedures performed were orthopedic (hip fracture repair and hip or knee arthroplasties) and exploratory laparotomies, with 68% receiving general anesthesia.

Predictors of postoperative deaths included history of congestive heart failure, coronary artery disease, neurologic disease or use of vasopressors intraoperatively; these same predictors were associated with nonfatal adverse outcomes along with a history of arrythmia and urgent/emergent surgery. Age, gender, type of surgery, and number of comorbid conditions were not associated with adverse outcomes by univariate analysis. Choice of general vs. regional anesthesia were not clearly associated with any difference in complications either. Further analysis by multivariate logistic regression models found that CHF, arrythmia, and history of neurologic disease increased the odds of any adverse postoperative event.

Increased hospital length of stay was predicted mainly by preoperative conditions (history of CHF, coronary artery disease, and cerebral vascular accidents) and urgent/emergent surgery. The fairly large number of adverse intraoperative events (91 events with 80 procedures, or 19% of patients) did not affect length of stay except for intraoperative vasopressor use. If a patient had a postoperative acute MI, CHF, arrythmia, or the need for a second operation the stay was also prolonged. Postoperative delirium was the most common neurologic adverse outcome, occurring in nearly 15% of the patients.

Discharge placements showed 55% went home and 45% went to skilled nursing facilities; the latter group was 33% more likely to have suffered a postoperative complication than the group discharged to home (15% complications). Liu et al note that the economic effect of these placements and the extra hospital days are significant, along with the unmeasured cost to caregivers and quality of life for the older patients.

In conclusion, they note that previous studies have not examined geriatric surgical outcomes related to intraoperative events, and the current review does not suggest any predictive associations except for the use of vasoactive agents. However, only nine of these events were observed out of 91 adverse events, so they acknowledge small numbers do not lead to strong conclusions. Liu et al urge that more studies be done to identify optimal management of CHF and cognitive dysfunction to improve postoperative outcomes, and that geriatric surgical patients without significant comorbidities be considered in a "low risk" group for cost-saving reductions in treatment and length of stay.

COMMENT BY MARY ELINA FERRIS, MD

With the fastest growing segment of the elderly population in the eighth decade of age and older, more medical research is needed for this group that has been previously neglected. Clinicians are often called upon to advise elderly patients and their families about surgical risks, and the preoperative history and physical is an important opportunity to adjust any modifiable health factors that could contribute to improved outcomes. It has long been known in geriatric medicine that age alone does not predict adverse surgical outcomes, but rather that the underlying state of health is more important. However, with advancing age the inevitable cumulative comorbidities make it difficult to distinguish a lower risk group since nearly all patients have some potential medical complications.

This study is aimed at establishing postoperative noncardiac surgical morbidity and mortality in patients aged 80 years and older in the current environment of improved perioperative care and outcomes. It originated in the department of anesthesia, so the emphasis was also on identifying any intraoperative and anesthetic management issues that might contribute to adverse outcomes, but its findings are interesting for all those who care for the elderly and are part of the decisions surrounding surgical choices and preparation.

Its weakness may be that the two hospitals studied are part of a prestigious medical school with many referral cases (although 1 hospital is more community-based than the other), biasing the sample toward a sicker or more complicated group of elderly patients. On the other hand, the intrahospital care delivered may have been superior to community hospitals that do not have the luxury of resident housestaff and the oversight of multiple faculty and geriatric services. Why the 1995 calendar year was chosen and not a more recent year was not explained; over the past five years, advances in treatment may make their conclusions less valid. Inpatient medical chart review as the only source of information has limitations and may not have provided complete

information on the patients, particularly when so much testing is performed in the outpatient setting and when many complications may occur after discharge.

The findings emphasize the importance of preoperative screening and treatment of any modifiable cardiac, pulmonary, and neurologic conditions. Age alone is not a predictor of adverse surgical outcomes, but rather the pre-existing state of health of the elderly person.

The high rate of postoperative delirium (15%), which prolonged the hospital stays by two days, merits further attention; at least one-third of the patients had preexisting neurologic disease but their mental status before surgery is unknown. Preoperative cognitive impairment has been shown in previous studies to increase the risk of in-hospital delirium,[1] which subsequently increases the risk of mortality and subsequent institutional placement. A large Danish study of 1218 noncardiac surgical patients older than age 60 showed an even higher rate of 26% postoperative cognitive impairment one week after surgery, which persisted in 10% three months later, most commonly in the oldest patients.[2] Future areas needing study include the role of pharmacologic agents and postoperative pain management in the etiology of these costly deliriums.

An accompanying article in the same issue from geriatric experts at RAND Corporation and UCLA identifies 21 target conditions in the vulnerable elderly for quality of care improvement.[3] Hospitalization and surgery ranked no. 6, with pharmacologic problems no. 1, and dementia and delirium no. 3. Clearly, all these areas need more attention for our older patients and will help us improve the care we deliver. ❖

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Pharmacology Update

Colesevel Hydrochloride Tablets (Welchol—Sankyo Parke Davis)

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

In june, the fda approved the first new bile sequestrant in many years. Colesevelam hydrochloride is a nonabsorbable polymer that has a high affinity for both trihydroxy and dihydroxy bile acids in the intestine. The drug prevents the reabsorption of bile acids, thus lowering LDL cholesterol. Colesevelam is distinguished from previous bile sequestrants such as cholestyramine and colestipol by having a lower incidence of gastrointestinal (GI) side effects. These side effects, along with the popularity and ease of use of statins, have limited their use in recent years. Sankyo Parke Davis, the company marketing the new sequestrant, is hoping to reverse that trend. Colesevelam is licensed from GelTex Pharmaceuticals, Inc., and will be marketed under the trade name Welchol.

Indications

Colesevelam is approved for use alone or in combination with an HMG-CoA reductase inhibitor as adjunctive therapy to diet and exercise for the reduction of elevated LDL-cholesterol in patients with primary hypercholesterolemia (Fredrickson Type IIa).[1]

Dosage

The recommended starting dose of colesevelam for monotherapy is three tablets taken twice daily with meals or six tablets once daily with a meal. The dose can be increased to seven tablets, depending upon the desired therapeutic effects.

In combination therapy (with a HMG-CoA reductase inhibitor), the recommended dose of colesevelam is three tablets taken twice daily with meals or six tablets taken once daily with a meal. Colesevelam should be taken with liquid.

It is supplied as 625 mg tablets.

Potential Advantages

Colesevelam appears to be well tolerated. GI side effects were generally not different among placebo groups and those taking doses ranging from 1.5 g to 3.75 g per day.[1,2] In contrast to other bile sequestrants, colesevelam binds to bile acids to produce a soft gelatinous-like material compared to the insoluble complexes that form from use of cholestyramine or colestipol. This physiochemical property of colesevelam is believed to significantly reduce the potential for GI side effects. Drug interactions with colesevelam are generally not problematic. No interactions have been reported with coadministration with digoxin, lovastatin, metoprolol, quinidine, valproic acid, or warfarin.[1]

Potential Disadvantages

The lipid-lowering effects of colesevelam are modest. LDL-cholesterol is reduced 15-19% from baseline, total

cholesterol from 7-10%, and HDL-cholesterol level increased from 3% to 11%.[1,2] There is a modest tablet burden, 6-7 tablets need to be taken daily.

Comments

Colesevelam is a nonabsorbed, water-absorbing polymer made of a polyallylamine cross-linked with epichlorohydrin and alkylated with 1-bromodecane and 5-bromohexyltrimethylammonium bromide.[2]

As with other bile sequestrants, these drugs interrupt the enterohepatic circulation of bile acids. Depletion of bile acids results in the increased conversion of cholesterol to bile acids by upregulation of cholesterol 7-alpha hydroxylase as well as increased numbers of LDL-receptors. This results in the decrease in serum cholesterol. Clinical studies indicate that the efficacy of colesevelam is similar to that of other bile sequestrants although there have been no published comparative studies. LDL-cholesterol reduction of up to 30% have been reported with high doses of cholestyramine (24 g/d) or colestipol (30 g/d); however compliance with these doses was generally poor.[4,5] A 16-21% reduction is a more realistic reduction with these agents.[5,6] The major advantages of colesevelam appear to be a lower potential for GI side effects and no apparent drug interactions. It is expected to be launched in the fall. Cost is not available at this time.

Clinical Implications

Bile sequestrants are useful as monotherapy in patients with moderately elevated LDL-cholesterol, particularly young adult men and premenopausal women as well as in combination therapy in more severe forms of hypercholesterolemia.[3] They have been shown to reduce cardiovascular mortality and morbidity.[4,7-9] GI side effects and drug interactions have limited their use. Colesevelam provides an alternative to other bile sequestrants as monotherapy or combination therapy with reduced potential for side effects and drug interactions. ❖

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CME Questions

5. The patient who has a predicted life expectancy of more than 10 years has been diagnosed with prostate cancer that is clinically localized. He consults both a radiation oncologist and a urologist regarding treatment options. Which one of the following statements is correct?

a. Both consultants will inform the patient that the anticipated result is about the same with either external beam radiation or radical prostatectomy.
b. The vast majority of urologists believe that radical prostatectomy is superior to external beam radiation.
c. The vast majority of radiation oncologists believe that radiation therapy is superior to radical prostatectomy.
d. None of the above

6. Which one of the following factors predicts increased hospital length of stay for noncardiac surgical patients aged 80 and older?

a. Urgent/emergent surgery
b. Episodes of hypotension during surgery
c. Site of surgery
d. Type of anesthesia

7. Which one of the following statements is correct?

a. The 30-day mortality rate following an uncomplicated course of postthrombolytic therapy is 10%.
b. The cost per life saved for hospitalizing a patient with an uncomplicated MI for longer than three days is $50,000.
c. The rate of ventricular arrythmia following thrombolytic therapy for acute MI drops dramatically after 48 hours.

8. Singh and colleagues found that calcium carbonate:

a. may interfere with the absorption of levothyroxine.
b. reduces T4 absorption.
c. increases thyrotropin levels.
d. All of the above

9. Which of the following statements is true about colesevelam?

a. Drug interactions with colesevelam are generally problematic.
b. Colesevelam is distinguished from previous bile sequestrants such as cholestyramine and colestipol by having a higher incidence of gastrointestinal (GI) side effects.
c. Colesevelam provides an alternative to other bile sequestrants as monotherapy or combination therapy with reduced potential for side effects and drug interactions.
d. Colesevelam should not be taken with liquid.

10. The major advantages of colesevelam appear to be a lower potential for GI side effects and no apparent drug interactions.

a. True
b. False

By Louis Kuritzky, MD

Cholesterol-Lowering, Dietary Treatment, and Psychological Function

The role of cholesterol lowering for prevention of cardiovascular disease went through a trying period during which there was concern expressed that pharmacologic reduction of cholesterol might have adverse psychological consequences. Some observational studies have found an association between depression, suicide, aggression and hostility and lower cholesterol levels. This study evaluated the psychological effect of implementing a cholesterol-lowering diet in 176 individuals with cholesterol levels of more than 198 mg/dL.

The group was divided into those receiving a low-fat diet, Mediterranean diet, and control diet. Diets were evaluated over a 12-week period, and in addition to physical and laboratory parameters, depression and anger were measured with the Beck Depression Inventory, Profile of Mood States. A variety of other psychometric tests were administered to assess stress, general health perceptions, and even perceptions of partners or close friends were included for analysis.

All groups had stable or improved psychological status throughout the study. Lipid changes were seen in both the participants in the low-fat diet group (5.1% cholesterol reduction) and Mediterranean diet (10% cholesterol reduction) compared with control. Wardle and colleagues conclude that their study does not demonstrate any adverse psychological effect from dietary cholesterol reduction. An adverse cognitive effect noted among the cholesterol-lowering diet groups seen during the trial was felt to be a chance event, but it is suggested that future trials seek further demonstration of the effect of cholesterol reduction on cognitive function. ❖

Wardle J, et al. Am J Med 2000;108: 547-553.

Risk of CHD Events After Menopause

Debate about the relative risks and benefits of postmenopausal hormone replacement therapy (HRT) continues unabated. The favorable effect of HRT upon traditional lipid fractions HDL, LDL is well established. Lipoprotein(a) (Lpa) is known to be an important risk factor for coronary heart disease (CHD), but has been dominantly studied in men, and usually in those without known coronary disease. This study examined the effects of HRT on Lpa in participants of the HERS trial (Heart and Estrogen/progestin Replacement Study), and the relationship with subsequent coronary heart disease end points.

This study evaluated 2763 postmenopausal women, measuring Lpa at baseline and at the conclusion of the trial (mean = 4.1 years). At baseline, the Lpa level of African American women was almost twice as high as other women. Baseline Lpa level was linearly associated with risk of subsequent CHD events.

HRT produced a significant reduction in Lpa, which was most evident in women with the highest levels of Lpa prior to treatment at baseline. Although the reduction in Lpa achieved with HRT did not reveal a significant association with reduced CHD events, a threshold effect was suggested by the fact that the women in the highest quartile of Lpa reduction did have a significantly lower risk of CHD events than those with smaller reductions. Though modulation of Lpa is not currently a commonplace therapeutic target, it is encouraging that women with highest deviations of Lpa from normal do demonstrate benefit from HRT. ❖

Shlipak MG, et al. JAMA 2000;283: 1845-1852.

Diagnosing OAD

The clinical diagnosis of obstructive airway disease (OAD) has not been systematically evaluated in rigorous blinded trials. Straus and colleagues evaluated 309 patients subgrouped into those with known chronic airway disease, suspected chronic OAD, and those free of either known or suspected OAD (asthma patients were excluded, so this was essentially a group of patients with consequences of chronic smoking). Among this group, they compared sensitivity, specificity, and likelihood ratios for spirometry-defined OAD (gold standard) with nine clinical factors, including history of chronic OAD, smoking history, presence of wheezing, maximum laryngeal height, minimum laryngeal height, and laryngeal descent.

Laryngeal height was measured as the distance from the suprasternal notch and the top of the thyroid cartilage. The difference between laryngeal height at end inspiration and end expiration was considered laryngeal descent.

Of the factors measured, only self-reported smoking history, self-reported history of chronic OAD, age, and maximum laryngeal height proved useful to discriminate OAD. Though previous studies have suggested a role for laryngeal descent, it was not found helpful in this trial, nor was wheezing. Straus et al acknowledge that spirometry should remain the diagnostic tool of choice, but suggest that their four described factors may facilitate a diagnosis of OAD in the absence of availability of spirometry. ❖

Straus SE, et al. JAMA 2000;283: 1853-1857.

In Future Issues: *Helicobacter pylori*—Keeping it in the Family