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Effects of ACE Inhibition on Cardiovascular Events in High-Risk Patients

ABSTRACT & COMMENTARY

Synopsis: *Treatment with ramipril appears to have protective effects on both the vasculature and the myocardium.*

Source: Yusuf S, et al. *N Engl J Med* 2000;342:145-153.

Epidemiologic and experimental data have clearly demonstrated that activation of the renin-angiotensin-aldosterone system plays an important role in increasing the risk of developing symptomatic and asymptomatic cardiovascular events.[1] Reduction of recurrent cardiovascular events has been clearly demonstrated in patients with known coronary artery disease (CAD)[1-3] independent of the ejection fraction, the etiology of the heart disease, diabetic status, concomitant use of medications, and regardless of whether hypertension was present. However, an adequately powered study evaluating the benefits of ACE inhibition in patients who are at high risk for cardiovascular events but who were not afflicted with left ventricular systolic dysfunction or heart failure had not been previously performed.

A double-blind, two-by-two factorial, randomized study was performed by 281 medical centers in Canada, the United States, western Europe, Argentina, Brazil, and Mexico. Yusuf and colleagues studied a total of 9297 high-risk patients who possessed evidence of vascular disease or diabetes plus one other cardiovascular risk factor (e.g., hypertension, elevated total serum cholesterol level, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria) and were not known to have a low ejection fraction or heart failure. These patients were randomized to receive either ramipril (10 mg once daily orally) or matching placebo for a mean of five years. The two-by-two factorial study evaluated both ramipril and vitamin E on the primary outcomes, which consisted of a composite of myocardial infarction (MI), stroke, or death from cardiovascular causes. The study was stopped early by the data and safety monitoring board because of the obvious benefits of ramipril and by the magnitude of the treatment effect. An overall reduction of 22% in

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the primary outcome of MI, stroke, or death from cardiovascular causes in patients who were not known to have a low ejection fraction or heart failure occurred. Treatment with ramipril appeared to have protective effects on both the vasculature and the myocardium and the benefit could not be ascribed solely to a rather small reduction in blood pressure that occurred.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

The renin, angiotensin, aldosterone system historically was thought to have important endocrine functions on salt and water retention, vasocontriction, release of aldosterone, and thirst. Although the system is activated in response to a decrease in intravascular volume or inadequate perfusion as a way of maintaining adequate blood flow, it is now recognized that this system operates in concert with an even more fundamentally complex tissue-based molecular signaling pathway involving angiotensin II. It now appears that the tissue activities of this system rather than the endocrine function alone are probably responsible for many of the structural and functional abnormalities that occur in the heart, vasculature, and kidneys during continued stimulation.[4] Inhibition of this system by first generation ACE inhibitors has clearly been demonstrated in numerous trials to significantly reduce the risk of future cardiovascular events.[5,6] The HOPE study demonstrates that the benefits of ACE inhibition exceed even our previous expectations. The beneficial effects on the vasculature, heart, and kidneys apparently go much beyond the rather small blood pressure-lowering effect of these drugs, suggesting that the pharmacological ability to block the untoward effects of the renin-angiotensin-aldosterone system permits the vasculature, heart, and kidneys to escape some of the ravages produced by long-term exposure to angiotensin and aldosterone. Precisely how these myocardial, vascular, and renal benefits occur will almost certainly be elucidated in future studies but, for the time being, there appears to be little question that ACE inhibition produced by ramipril in the HOPE study was successful in dramatically decreasing rates of death, MI, and stroke even in patients who were not afflicted with serious cardiovascular problems.

It now appears reasonable to consider prescribing ramipril for high-risk patients with a history of CAD, peripheral vascular disease, stroke, or diabetes mellitus since most of these patients will have at least one additional cardiovascular risk factor as required by patients enrolled in the HOPE study. This approach will greatly broaden the spectrum of patients who can be treated effectively with ACE inhibition assuming there are no clear contraindications to these agents or signs of drug intolerance. There are currently additional large-scale studies taking place such as the Prevention of Events with ACE Inhibition (PEACE) study and the European Trial of Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) studies. These two large clinical trials are somewhat similar to the HOPE study, however, unless the results of these studies absolutely contradict the HOPE results, the results of this landmark study of 9000 patients will be difficult to ignore and will almost certainly lead to an increase in the appropriate use of ACE inhibition in high-risk patients without manifest CAD. ❖

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Managing Dyslipidemia in Older Adults

ABSTRACT & COMMENTARY

Synopsis: *Evidence supports aggressive control of lipid disorders in persons older than age 65 up to age 85 since elevated LDL and total cholesterol are independent risk factors for coronary events. Diet, lipid-lowering medications, exercise, and weight loss may show results within 2-5 years of initiation and can decrease the risk of coronary events by up to 45%.*

Source: Carlsson CM, et al. *J Am Geriatr Soc* 1999;47: 1458-1465.

Literature review of clinical trial data limited exclusively to subjects older than 65 years of age was summarized to evaluate both the importance of dyslipidemia as a risk factor for coronary heart disease (CHD) and the safety and efficacy of lipid-lowering interventions in this age group. Limited data for persons older than age 85 required the conclusions to be restricted to those younger than age 85. Women were included in many of the studies and some studies suggest that these conclusions may be even more significant for them than for men in this same age group.

Lipid and CHD risk associations in the elderly now appear to be supported by several studies. Recent data from the Framingham Heart Study (2051 participants > age 65 and 5209 aged 40-70 years) show that total cholesterol more than 306 mg/dL independently predicted future myocardial infarctions (MIs) and CHD deaths. High LDL levels were also associated with higher mortality, although this risk diminished with age. High HDL was associated with lower death rates across all age groups. A Kaiser Permanente study of 2746 men between ages 60-79 also showed the link between elevated lipids and increasing excess risk of CHD death with increasing age. No risk was initially suggested in one large epidemiologic study (EPESE) involving 6566 older adults and 40,666 total participants followed for seven years, but further analysis showed that comorbid conditions in persons approaching death had caused reductions in cholesterol levels, confusing the calculations. When these were excluded, the association between CHD death risk and elevated total cholesterol was significant at 1.57 relative risk.

Whether lowering lipid levels in the elderly is effective and safe is supported by literature showing exercise programs (e.g., 30-40 minutes aerobic exercise 3 times weekly for 12 weeks) that can improve HDL cholesterol up to 19% and decrease total cholesterol 6%; however, these changes may reverse when the exercise program is stopped. Weight loss is probably more significant, lowering total cholesterol levels 5%-20% through low fat, low cholesterol, and high-fiber diets, although malnutrition from excessively limited diets is also a concern in this age group.

Drug therapy is probably most effective, using HMG-CoA reductase inhibitors (statins), which studies show to be well tolerated in this age group. Five studies are reviewed with elderly subjects numbering from 142 to 1021 showing total cholesterol reductions from 17%-26%, and LDL reductions up to 36%. Estrogen replacement therapy for women can also lower total cholesterol to 14% and LDL to 24%. Side effects for these medications do not appear to be any more adverse than for younger patients.

Benefits of the lipid lowering are seen most clearly in older persons with known CHD; up to 28% in reduction of total mortality is seen compared to controls not treated. Another group of 1283 subjects older than age 65 in a randomized, double-blind, statin study for five years after acute MI showed 45% less cardiac death and 40% less stroke rate. For estrogen replacement, the ongoing HERS study has not yet demonstrated a benefit in subsequent CHD events.

For primary prevention of CHD events in persons without known pre-existing disease, studies are more controversial. One study that did show a benefit did not include elderly persons, and another showed a 28% lower incidence in major coronary events in those older than age 65 with average total cholesterol and below average HDL levels. The FAME trial using randomized Fluvastatin and diet aimed at ages 70-85 is now recruiting participants and will hopefully provide more guidance in the future.

Carlsson and colleagues conclude that fasting lipid levels should be used as screening tests, with therapy instituted as appropriate, for all persons younger than age 85 unless comorbid conditions would preclude even a short-term effect (2-5 years). National NCEP guidelines for lipid reduction should be followed (recently reviewed and reaffirmed: targeting a goal of LDL 130 mg/dL for primary prevention and < 100 mg/dL for known CHD secondary prevention).[1,2] Diet and exercise should be given a four- to six-week trial and medications added as needed. For persons with known CHD, med-

ications may be started as first-line therapy along with diet and exercise for a proven benefit of decreased risk of cardiac death, recurrent MI, and need for revascularization procedures.

COMMENT BY MARY ELINA FERRIS, MD

Given that CHD is the leading cause of mortality in older adults and an enormous source of hospital activity and expense, this summary of possible preventive strategies provides a useful guide. Although not all therapies that have been shown to work in younger populations can automatically be translated to the elderly, in this case the literature appears to support the efficacy of reducing CHD risk and mortality (and stroke risk) through lipid reductions even up to age 85, without published differences in medications' adverse effects. An additional geriatric consideration that must be weighed in all newly initiated therapies is the effect on quality of life; i.e., if the person's life expectancy from other illnesses is no greater than two to five years, the potential for causing more harm from the lipid-lowering treatment outweighs the possible benefit. Otherwise, it appears from this review that significant gains in CHD reductions are possible with more widespread management of dyslipidemia, particularly in older persons with pre-existing disease.

Clinicians who adopt more frequent monitoring of lipids should be prepared to find many abnormal results: up to 50% of persons older than age 65 qualify for dietary therapy and 10%-25% for pharmacotherapy in national nutritional surveys. The high frequency of dyslipidemia in older persons appears to be an aging-associated phenomenon and is not completely understood, possibly related to lipoprotein metabolism and hormonal changes. LDL cholesterol levels increase from puberty onward and even more for women after menopause. With aging, the clearance of LDL and the number of hepatic receptors decrease.

One area this article did not address is the importance of diabetes as a comorbidity and accelerator of lipid disorders, an extremely common problem in the elderly. New guidelines from the American Diabetes Association[3] also urge more aggressive treatment of dyslipidemia to a goal of LDL less than 100 mg/dL, putting all persons with diabetes in the same category as those with pre-existing CHD. Although the diabetes guidelines do not specifically address treatment of the elderly, it would seem prudent from this article to also pursue abnormal lipids in elderly persons with diabetes as though they had known heart disease. ❖

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Melatonin for Insomnia During Benzodiazepine Discontinuation

ABSTRACT & COMMENTARY

Synopsis: *Garfunkel and associates conclude that controlled-release melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality.*

Source: Garfinkel D, et al. *Arch Intern Med* 1999;159: 2456-2460.

Benzodiazepines are commonly used for treating insomnia but are not recommended for chronic use. However, many patients take benzodiazepines for longer than recommended periods and have problems such as rebound insomnia while discontinuing therapy. The current study investigates the use of melatonin, a hormone that promotes normal sleep in humans, to facilitate benzodiazepine discontinuation. Thirty-four subjects receiving benzodiazepine therapy were enrolled in the two-period study. In period one, patients received 2 mg of controlled-release melatonin or placebo in double-blinded fashion for six weeks. Subjects were encouraged to reduce their benzodiazepine dosage by 50% during week 2, 75% during weeks 3 and 4, and to discontinue benzodiazepine therapy completely during weeks 5 and 6. In period two, all subjects received melatonin in single-blinded fashion for six weeks and attempts to discontinue benzodiazepine therapy were resumed. Benzodiazepine use and subjective sleep-quality scores were reported daily by all patients. Subjects were then allowed to continue melatonin therapy and follow-up reassessments were performed six months later.

After period one, 14 of 18 subjects who had received melatonin therapy discontinued benzodiazepine therapy compared to four of 16 in the placebo group ($P = 0.006$). Sleep-quality scores were significantly higher in the melatonin therapy group ($P = 0.04$). Six additional subjects in the placebo group discontinued benzodiazepine

therapy when given melatonin in period two. Good sleep quality was maintained in 19 of 24 patients who discontinued benzodiazepine and received melatonin therapy, as reported during the six-month follow-up. Melatonin therapy was well-tolerated by all subjects, with adverse effects being minimal and comparable in both groups (2 melatonin-treated subjects and 1 placebo-treated subject reported headaches). Garfunkel and associates concluded that controlled-release melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality.

COMMENT BY MICHAEL F. BARBER, PharmD

Many patients receive chronic benzodiazepine therapy for a variety of disorders, including anxiety disorders and sleep disorders. While the benzodiazepines are relatively safe and effective agents, their long-term use is not recommended for reasons such as tolerance and abuse potential. Thus, clinicians often may wish to discontinue the benzodiazepines in some patients. Although careful titration (i.e., reducing the total daily dose of the benzodiazepine by approximately 25-50% weekly) can help minimize such complications such as rebound anxiety and other related withdrawal symptoms, insomnia is a ubiquitous problem in patients undergoing benzodiazepine discontinuation. While some medications such as diphenhydramine and trazodone may help treat this insomnia, these agents often fail or are intolerable to some patients. Melatonin is a logical agent to evaluate for this purpose since the chronic use of benzodiazepines can suppress the endogenous release of melatonin during the normal burst hours. This may be due to a disruption of the normal sleep-wake cycle based upon circadian rhythm. Thus, the use of melatonin may actually serve to correct the disruption of the sleep-wake cycle, allowing for normal sleep patterns to continue.

This study of the use of melatonin for insomnia in patients undergoing benzodiazepine discontinuation was conducted in a relatively small number of patients; thus, the results should be considered as preliminary evidence. It is important to note that the role of melatonin in these patients is to treat insomnia, thereby facilitating benzodiazepine discontinuation. However, melatonin cannot prevent benzodiazepine withdrawal symptoms and thus does not eliminate the necessity of gradual dose reduction in patients who have been receiving benzodiazepines for an extended period of time. However, the use of melatonin may overall lead to better patient adherence to benzodiazepine discontinuation. (*Dr. Barber is Assistant Professor of Clinical Sciences and Administration, University of Houston College of Pharmacy, Houston, Texas.*) ❖

Supine Position Increases Pneumonia Risk in Ventilated Patients

ABSTRACT & COMMENTARY

Synopsis: *Medical and respiratory ICU patients who were managed in the semirecumbent (45° head up) position had a lower incidence of nosocomial pneumonia than patients managed supine, especially if they received enteral feedings.*

Source: Drakulovic MB, et al. *Lancet* 1999;354(9193): 1851-1858.

In this study from the university of barcelona, Drakulovic and colleagues randomized intubated, mechanically ventilated patients to be managed in either the supine (0° head elevation) or the semirecumbent position (45° head elevation) to determine the effect of position on development of ventilator-associated pneumonia. The study was done in one respiratory ICU and one medical ICU, and included all patients ventilated during the study period unless they had had recent abdominal surgery, recent neurosurgical intervention, refractory hypotension, or intubation within one month of entry. All management except for body position was at the discretion of the primary physician.

Eighty-six patients completed the trial at the time it was halted by interim analysis—39 who were nursed in the semirecumbent position and 47 who were nursed supine. The groups were well matched in terms of age (mid-60s), gender (75% male), APACHE II score (about 23), and the cause of acute respiratory failure; one-third of the patients in each group had acute exacerbations of chronic obstructive pulmonary disease. Mean duration of mechanical ventilation was similar in the two groups (171 vs 145 hours in semirecumbent vs supine positions, respectively), as was mean ICU stay (9.7 vs 9.3 days).

The clinical suspicion of pneumonia was determined in a standard fashion, and microbiological confirmation was sought by tracheal aspirate, bronchoalveolar lavage (BAL), or bronchoscopic protected specimen brush (PSB) at the discretion of the clinician. Colony-count thresholds for diagnosing pneumonia were those in widespread use: 10^5 colony-forming units (CFU)/mL for aspirates, 10^4 CFU/mL for BAL, and 10^3 CFU/mL for PSB.

The frequency of clinically suspected nosocomial pneumonia was lower in the semirecumbent group than in the supine group (3/39 vs 16/47 patients; 95% confidence interval [CI] for difference 10-42; P = 0.03). A similar dif-

ference was found with respect to microbiologically proven pneumonia (2/39 vs 11/47 patients; 95% CI 4-32; P = 0.018). Patients receiving enteral nutrition were more likely to develop pneumonia (odds ratio 5.7, 95% CI 1.5-33; P = 0.013), and 50% of all patients who were managed supine and also received enteral feeding developed pneumonia. There were no statistically significant differences in ICU mortality between the semirecumbent (7/39, 18%) and supine (13/47, 28%) patients; there was also no difference in overall mortality in patients with pneumonia (either suspected or confirmed) vs. those without pneumonia.

COMMENT BY DAVID J. PIERSON, MD, FACP, FCCP

Previous studies have shown that mechanically ventilated patients who are managed in the semirecumbent position tend to reflux and aspirate gastric contents less frequently than those managed supine. These are major predispositions to development of ventilator-associated pneumonia, so it stands to reason that the head-up position would be associated with a lower incidence of this complication. However, this is the first randomized, controlled trial to demonstrate this lower incidence.

Other predispositions to ventilator-associated pneumonia include depressed level of consciousness (and the incidence was inversely proportional to Glasgow Coma Scale score in the present study), increased severity of illness, increased duration of mechanical ventilation, and enteral vs. parenteral nutritional support. The clinician has control of only some of these things, and a relatively simple intervention such as elevating the head of the bed is one of them. It is noteworthy that not all ventilated patients are candidates for management in the semirecumbent position, and that even among those patients who met the entry criteria for this study nearly one-third had to be excluded. Nevertheless, in patients with no contraindication to the head-up position, it seems a reasonable thing to do when possible. (*Dr. Pierson is Professor of Medicine, University of Washington, Medical Director, Respiratory Care, Harborview Medical Center, Seattle.*) ❖

Pharmacology Update

Gatifloxacin Tablets and Injection (Tequin, Bristol-Myers Squibb)

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

A new extended spectrum fluoroquinolone antibiotic has been approved by the FDA. Bristol-Myers Squibb's gatifloxacin (Tequin) is an 8-methoxy-fluoroquinolone similar to moxifloxacin (Avelox). Gatifloxacin has activity against gram-positive, gram-negative, and atypical pathogens and is available in both oral and parenteral forms. The drug has a wide range of indications including upper and lower respiratory tract infections and urinary tract infections (UTIs).

Indications

Gatifloxacin is approved for the treatment of adults with the following infections caused by susceptible strains of microorganisms:[1] acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *H. parainfluenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*; acute sinusitis due to *S. pneumoniae* or *H. influenzae*; community-acquired pneumonia due to *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *S. aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella* pneumophilia; uncomplicated or complicated UTIs due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*; pyelonephritis due to *E. coli*; and uncomplicated urethral gonococcal infections in men or cervical gonorrhea or acute, uncomplicated, rectal infections in women due to *Neisseria gonorrhoeae*.

Dosage

The recommended daily dose of gatifloxacin is 400 mg once a day for 7-10 days for acute bacterial exacerbation of chronic bronchitis, complicated infectious UTIs, and acute pyelonephritis. The duration of therapy is 7-14 days for community-acquired pneumonia, and 10 days for acute sinusitis. For uncomplicated UTIs (e.g., cystitis) or uncomplicated urethral gonorrhea in men or endocervical or rectal gonorrhea in women the dose is 400 mg as a single dose.[1] For uncomplicated UTIs, 200 mg daily for three days is an alternative regimen.

Gatifloxacin may be taken without regard to food including milk and dietary supplements containing calcium.[1] However, it should be taken at least four hours before products containing iron, zinc, or magnesium. These include antacids, multivitamins, and buffered products such as Videx.[1,4]

The absolute bioavailability of gatifloxacin is 96% and the oral and intravenous forms are interchangeable on a milligram basis. The injection should be administered by intravenous infusion only.[1]

In patients with impaired renal function (creatinine clearance < 40 mL/min) the initial dose should be 400 mg followed by 200 mg daily. Single-dose regimens do not need to be reduced.[1]

Gatifloxacin is marketed as 200-mg and 400-mg

tablets and 200-mg (10 mg/mL, 20 mL) and 400-mg (10 mg/mL, 40 mL) single-use vials.

The drug is not for use in children younger than age 18.

Potential Advantages

In vitro studies indicate that gatifloxacin is more active against *S. pneumoniae* compared to levofloxacin. As with other quinolones, the MICs are not affected by susceptibility to penicillin.[2] Gatifloxacin is highly selective in the inhibition of bacterial topoisomerases and has low activity against mammalian topoisomerase.[5]

Potential Disadvantages

Gatifloxacin is less active than ciprofloxacin against *Pseudomonas* species.[3] Gatifloxacin may prolong the QTc interval in some patients. In normal volunteers (n = 55) the mean change in QTc was 2.9 ± 16.5 msec.[1] It should be avoided in patients at risk for prolongation of QTc such as those taking class IA and III antiarrhythmics or drugs that may have the potential to prolong QTc (e.g., erythromycin, cisapride, antipsychotics, tricyclic antidepressants).[1] Most common side effects include nausea (8%), diarrhea (4%), headache (4%), and dizziness (3%).[3]

Comments

Gatifloxacin is a new extended-spectrum fluoroquinolone with activity against gram-positive and gram-negative pathogens and anaerobes. It is slightly less active than ciprofloxacin against Enteriobacteriaceae, and less active than ciprofloxacin against *P. aeruginosa*.[3] Gatifloxacin penetrates well into respiratory and reproductive tissue with the tissue/serum ratio of 1 or greater[1,3] and has a negligible effect on P450 isoenzymes (CYP) and apparent low potential for phototoxicity. Comparative clinical trials have not been published in detail, but are available in abstract form.[3] These limited data suggest that gatifloxacin (400 mg daily for 7-14 days) is similar to clarithromycin (500 mg twice daily for 7-14 days) in the clinical cure of community-acquired pneumonia (95% vs 93%). In acute maxillary sinusitis clinical cure was similar to clarithromycin (93% vs 90%). As a single dose of 400 mg or 200 mg/day for three days, the clinical cure rate is similar to ciprofloxacin (100 mg twice daily for 3 days) in uncomplicated UTI (93% vs 95% vs 93%). In the treatment of gonorrhea, gatifloxacin (400 mg as a single dose), bacterial eradication was similar to ofloxacin (400 mg as a single dose) (≥ 99%). In a subset analysis, gatifloxacin (400 mg daily for 7-10 days) was reported to be more efficacious (i.e., clinical cure) than cefuroxime axetil (250 mg twice daily for 7-10 days) in the treatment of acute exacerbation of chronic bronchitis (89% vs 77%).[3]

Gatifloxacin 400 mg daily cost about $7 or $70 for a 10-day regimen.

Clinical Implications

Gatifloxacin is the sixth and most recent fluoroquinolone to be approved for respiratory tract infections, joining levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, and moxifloxacin. Grepafloxacin has been withdrawn from the market while trovafloxacin has been associated with liver toxicity and sparfloxacin with phototoxicity. Prolongation of the QT interval has become a class warning although the FDA concedes that the effect may vary with different agents.[6] It is not clear if one of the newer 8-methoxyfluoroquinolones would emerge as an ideal "respiratory" quinolone replacing levofloxacin, which has the most clinical experience. Levofloxacin recently gained FDA approval for the treatment of penicillin-resistant *S. pneumoniae* in patients with community-acquired pneumonia.

These quinolones should be prescribed prudently in order to prevent development of resistant strains of bacteria. Evidence of *S. pneumonia* with reduced susceptibility to fluoroquinolones has already been reported.[7,8] ❖

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CME Questions

20. Which of the following groups are recommended to have their LDL cholesterol levels decreased below 100 mg/dL to achieve proven risk reduction in coronary heart disease?

a. Males age 40-60 without known disease.
b. Females age 65-85 after menopause.
c. Males age 65-85 with previous coronary disease.
d. Diabetic males older than age 85.

21. Which is *not* true about gatifloxacin?

a. It is dosed twice a day.
b. It is available in both oral and parenteral forms.
c. It can be given as a single dose for uncomplicated UTIs and gonorrhea.
d. It is approved for the treatment of community-acquired pneumonia caused by penicillin-resistant *S. pneumoniae*.

By Louis Kuritzky, MD

Testosterone Supplementation in the Aging Male

The role of testosterone in achieving and maintaining erections in sexual settings (as opposed to "central" erections occurring spontaneously in a cyclic fashion throughout the day and night) remains uncertain. Men who are deficient in testosterone may suffer ED, which may respond to testosterone supplementation, but the frequency of testosterone deficiency as a cause of ED in aging men is extremely low, typically less than 5%.

Much of the population of senior men who demonstrate low testosterone levels suffer from other significant health problems, and it is unclear whether these additional disorders are precipitants for the decline in testosterone levels. Since testosterone supplementation is not without consequence (economic costs, exacerbation of BPH, induction or exacerbation of prostate cancer, worsened lipid profile risk patterns), it is important to ascertain the (potential) value of such supplementation.

Overt hypogonadism is found in only about 4% of men over age 40-70, if defined as both low testosterone and high gonadotropins. If levels of bioavailable testosterone are the measurement designated to define clinically relevant hypogonadism, as many as 35% of men over age 60 will be hypogonadal and may benefit from testosterone supplementation.

Kim suggests that in clinical settings where symptoms suggest hypogonadism, testosterone supplementation may be considered; dosages should provide a serum testosterone level of at least 240 ng/dL. There is an important need for a large, long-term trial to ascertain the risk-benefit relationship of testosterone supplementation in the elderly. ❖

Kim YC. Int J Impot Res 1999;11: 343-352.

Task Force V: White-Coat Hypertension

It is not uncommon for some patients to manifest an elevation of blood pressure only in a medical setting, a circumstance variously designated as white-coat hypertension (WCH), isolated office hypertension, clinic hypertension, and other names. The most common definition is the presence of consistently elevated blood pressure measured in the office, in the company of consistently normal blood pressure measured in nonmedical settings. Similarly, the term "white coat effect" has been coined to indicate the difference between measured ambulatory blood pressure.

WCH is present in about 20% of individuals designated as having hypertension. The magnitude of the white-coat effect appears to increase with increasing age, and disproportionately involves systolic blood pressure; that is, the lower blood pressure found at home is primarily a difference in systolic measurements, while diastolic pressure shows substantially less variation.

Whether target organ damage results from WCH is a matter of debate, but the predominance of information suggests little measurable consequences in such important realms as left ventricular hypertrophy. On the other hand, WCH is associated with microalbuminuria, albeit to a lesser degree than sustained hypertension.

Overall morbidity and mortality for WCH is small on an absolute basis, being minimally to only modestly increased compared to normals, and never approaching the magnitude of frankly hypertensive patients.

A final consensus on the consequences of WCH remains to be achieved. Since a substantial minority of WCH patients go on to have sustained hypertension in a fairly brief time period (11-37% over 3-5 years), patients with WCH are recommended to undergo follow-up on an indefinite basis. ❖

Pickering TG, et al. Blood Press Monit 1999;4:333-341.

Results of Outpatient Multidisciplinary Pulmonary Rehabilitation

The benefit of pulmonary rehabilitation for COPD has been demonstrated in meta-analysis to be beneficial over the short term (i.e., < 6 months). This trial, on the other hand, investigated long-term effects of pulmonary rehabilitation on use of health services, talking, and overall health status.

To be included in the study, patients must demonstrate an FEV_1 less than 60% predicted, with less than 20% reversibility after bronchodilator (beta-agonist), in stable condition for at least two months. Rehabilitation included occupational therapy, physiotherapy, diet counseling, and assistance with smoking cessation. Visits were arranged three times weekly for six weeks. Measurement of walking was done by the 10-meter shuttle-walk test; overall health status was measured by the SF-36.

Though not a primary end point of the study, relative risk of death in the treatment group was 0.5 when compared to the control (usual care) group. Pulmonary functions were equal in both groups. Although equal numbers of persons were admitted to the hospital from both groups, the actual number of admissions and number of days spent in the hospital was significantly less for the treated group. Walking, breathlessness, and overall health-status outcomes were more favorable in the treatment group. Griffiths and colleagues conclude that pulmonary rehabilitation should be incorporated into the traditional algorithm for long-term COPD management. ❖

Griffiths TL, et al. Lancet 2000; 355:362-368.

In Future Issues: Does a High Salt Intake Increase Your Risk for Stroke?