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## Colon Polyps, Flexible Sigmoidoscopy and Colon Cancer Screening

ABSTRACTS & COMMENTARY

***Synopsis:*** *Patients with an advanced distal adenoma are twice as likely to have an advanced proximal adenoma as patients with a non-advanced distal adenoma.*

**Sources:** Schoen RE, et al, for the Polyp Prevention Trial. *Gastroenterology* 1998;115:533-541; Ahlquist DA. *Gastroenterology* 1998;115:777-786.

In this large study performed at multiple centers throughout the United States, Schoen and colleagues sought to evaluate the clinical significance of small tubular adenomas with low-grade dysplasia, found on flexible sigmoidoscopy. The study was performed on 981 subjects who were found to have distal adenomas at colonoscopy before randomization in the Polyp Prevention Trial. Among these, 47% had at least one distal adenoma that was regarded as pathologically advanced, 22% had a proximal adenoma, and 4% had an advanced proximal adenoma. While an advanced proximal adenoma was more likely to be found in a patient with an advanced distal adenoma than in a patient with a non-advanced distal adenoma (5.9% vs 2.9%; P = 0.03), 15 of 42 advanced proximal adenomas would have been missed among patients with a non-advanced distal adenoma if colonoscopy had not been performed. Schoen et al conclude that patients with an advanced distal adenoma are twice as likely to have an advanced proximal adenoma as patients with a non-advanced distal adenoma. However, failing to proceed to colonoscopy in patients with a non-advanced distal adenoma would result in not detecting a sizeable percentage of the prevalent advanced proximal adenomas. They felt that these data supported the performance of colonoscopy in patients with a non-advanced distal adenoma.

The accompanying editorial provides an excellent review of the role of flexible sigmoidoscopy in colon cancer screening, emphasizes several important points, and concludes that, while flexible sigmoidoscopy is an excellent tool for screening recto-sigmoid neoplasms, it is insensitive and ineffective for the detection of proximal colon neoplasms and that consideration should be given to screening techniques that evaluate the entire colon.

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## INSIDE

**COMMENT BY EAMONN M.M. QUIGLEY, MD**

The role of screening in the detection of colorectal cancer and in preventing mortality related to this common malignant disease is now established, and protocols for colon cancer screening have been promulgated by several professional organizations, health care providers, and government agencies. Flexible sigmoidoscopy, in particular, has been advocated as playing a central role in national colon cancer screening programs and will undoubtedly be frequently performed by primary care physicians for this reason. This paper and the accompanying editorial address a number of important issues regarding the issue of flexible sigmoidoscopy in colorectal cancer screening. The data from the polyp prevention trial provide insights into the significance of polyps of various histological grade detected at flexible sigmoidoscopy. While previous studies have clearly demonstrated that all polyps visualized on flexible sigmoidoscopy should be biopsied, the clinical interpretation of polyp histology has been somewhat controversial. While nobody would dispute the non-significance of hyperplastic polyps, some have suggested that patients could be selected for full colonoscopy based on the degree of dysplasia within the resected polyp. This study clearly demonstrates that, while those with high-grade polyps within the range of a flexible sigmoidoscopy are more likely to have high-grade polyps more proximally, the presence of "low grade" histology in a distal polyp does not protect against "high grade" proximal polyps. The simple conclusion from this study, therefore, is that all patients found to have an adenomatous polyp on flexible sigmoidoscopy should undergo colonoscopy. Ahlquist's careful and thoughtful editorial raises several additional issues. He first argues that there is little or no evidence to suggest that flexible sigmoidoscopy is a useful screening tool for proximal colon cancer. In support of this, he points out that, if colonoscopy was based exclusively on the finding of a recto-sigmoid adenoma at flexible sigmoidoscopy, approximately 70-80% of all proximal cancers would be missed. Additionally, by careful analysis of the data from this study, he suggests that, while using sigmoidoscopic findings to triage colonoscopy may increase the likelihood of finding a proximal adenoma on subsequent colonoscopy, it does so at the expense of sharply reducing its already low sensitivity and screening efficacy for proximal neoplasia. The lessons for the physician performing screening flexible sigmoidoscopy appear straightforward. Flexible sigmoidoscopy is a valuable tool for the detection of recto-sigmoid polyps and has an important role to play in the prevention of rectosigmoid carcinoma; however, it does not have a significant effect on the detection or prevention of more proximal polyps or tumors. This begs the inevitable question to which we do not, as yet, have the answer: Should colonoscopy be the screening technique of choice? ❖

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# Bundle Branch Block Revisited

ABSTRACT & COMMENTARY


***Synopsis:*** *Bundle branch block is a marker of a slowly progressive degenerative disease that affects the myocardium.*


**Source:** Eriksson P, et al. *Circulation* 1998;98:2494-2500.

Conflicting data exist concerning the etiology and significance of bundle branch block (BBB) on the electrocardiogram (ECG). Thus, Eriksson and colleagues recorded 12-lead ECGs in a random sample of 855 men who were 50 years old in 1963 when they were recruited in the city of Goteborg, Sweden, and followed them for 30 years with periodic examinations.

During the 30 years, 82 subjects with BBB were found (10%). Most acquired BBB after entry; only 1% had BBB at entry. BBB became more prevalent with aging. At age 75 years, right BBB was four times more prevalent than left BBB (39 vs 9%). ECG evidence of left ventricular hypotrophy preceded left BBB in one-quarter of the subjects vs. 6% for right BBB. Risk factors for atherosclerosis, myocardial infarction (MI), and a diagnosis of ischemic heart disease were no different between those who developed BBB and those who did not. However, cardiomegaly on chest x-ray ($P < 0.05$) and congestive heart failure (36% BBB vs 14% of controls; $P < 0.01$) were more common with BBB. Also, among those who died of cardiovascular causes, more subjects had a history of chronic heart failure with BBB (61%) vs. no BBB (28%; $P < 0.01$). Eriksson et al conclude that BBB is a marker of a slowly progressive degenerative disease that affects the myocardium.

### COMMENT BY MICHAEL H. CRAWFORD, MD

This study is consistent with the old adage that BBB is more commonly associated with cardiomyopathy rather than coronary artery diseases (CAD). In fact, no relation could be established between BBB and risk factors for atherosclerosis or overt CAD. This is consistent with other studies and the observation that BBB is not usually caused by acute MI. Also, the prevalence of BBB is highly correlated with advancing age, being 1% at age 50 and 17% at age 80 in men. Thus, CAD and BBB often coexist and this combination is known to increase mortality in acute MI and chronic CAD patients. Other studies suggest this may be due to a greater propensity to ventricular arrhythmias and sudden death, possibly due to prolonged repolarization. However, acute MI superimposed on a chronic progressive cardiomyopathy may result in a higher than expected mortality due to pump failure.

The major limitation of this study was that the small number of patients with BBB reduced the power for comparing left to right BBB, which many believe are of different significance. Also, ECGs were only recorded every 5-17 years, so details about the onset and potential causes of BBB are hard to decipher. In addition, there are few objective data about other cardiac diseases in this study. Nor are there electrophysiologic data about the site of block or the need for pacing. The implications of this study are that patients who develop or present with BBB should have an echocardiogram done to assess left ventricular function. The need for stress tests or coronary angiography is less clear in the absence of other indications for these procedures. (*Dr. Crawford is Robert S. Flinn Professor, Chief of Cardiology, University of New Mexico, Albuquerque.*) ❖

# Miglitol Reduced Cardiovascular Events, Hypoglycemia, and Weight Gain in Older Type 2 Diabetics

ABSTRACT & COMMENTARY

***Synopsis:*** *Treatment with miglitol offers older type 2 diabetic patients a useful and relatively safe therapeutic option for the treatment of their diabetes.*

**Source:** Johnson PS, et al. *J Clin Endocrinol Metab* 1998; 83:1515-1522.

Selecting a hypoglycemic agent for the treatment of type 2 diabetes is not as "clear cut" as it may seem. Recent major reports from the United States[1] and the United Kingdom[2] support the effort to reduce blood glucose and HbA1c to as near the normal range as possible. This approach has resulted in the reduction of microvascular disease (blindness, renal failure, etc.) but not in a significant reduction in ischemic heart disease and stroke (macrovascular disease). When insulin and sulfonylurea preparations have been used, there has been weight gain and an increase in the number of cardiovascular risk factors.

The use of the alpha-glucosidase inhibitors, such as acarbose and miglitol, has gradually been increasing because they reduce postpyrandial blood glucose rises and do not cause hypoglycemia, which can be a significant problem in older patients.

Johnson and associates have published a one-year study to determine the safety, efficacy, and tolerability of the alpha-glucosidase inhibitor miglitol as compared to the sulfonylurea glyburide in the treatment of patients with type 2 diabetes who were older than 60 years of age and inadequately controlled by diet alone.

Four hundred diet-treated patients were randomized to receive either placebo tid (n = 101), miglitol 25 mg tid (n = 104), miglitol 50 mg tid (n = 102, or glyburide once daily, titrated based on fasting plasma glucose (n = 104) for a period of 56 weeks. They assessed efficacy based on HbA1c, fasting, and post-prandial glucose, insulin, and lipid levels as well as 24-hour urinary excretion of glucose and albumin.

At the one-year end point, HbA1c treatment effects (placebo-subtracted change in HbA1c from baseline) were -0.49% for miglitol 25 mg, -0.40% for miglitol 50 mg, and -0.92% in the glyburide group. Hypoglycemia occurred in 8% of the placebo group, 10% and 9% of the

25 mg and 50 mg miglitol group, and in 46% of the glyburide group. Weight gain was significantly greater in the glyburide-treated group (mean increase 5 lbs). Total cardiovascular events were reduced in the miglitol group, with 22% of the placebo group experiencing a cardiovascular event as compared to 18% on 25 mg miglitol, 17% on 50 mg miglitol, and 29% of those receiving glyburide.

Diarrhea, flatulence, and nausea were significantly more frequent in the miglitol group but were often temporary. There were no significant differences between treatment groups of discontinuation due to adverse events (6% placebo, 10% miglitol 25 mg, 12% miglitol 50 mg, and 6% glyburide). The most common reasons for discontinuation were hyperglycemia, diarrhea, and flatulence in the miglitol patients and cardiovascular events in the glyburide group.

Treatment failure was significantly lower in the glyburide group (2%) than in the other three groups—11% for placebo and miglitol 25 mg and 6% for miglitol 50 mg.

Treatment responders defined as patients who demonstrated a reduction in HbA1c from baseline to end point of at least 1% or whose end point was 7% or less were 33% of the miglitol 25 mg, 30% of the miglitol 50 mg, and 52% of the glyburide patients were responders.

Treatment with miglitol offers older type 2 diabetic patients a useful and relatively safe therapeutic option for the treatment of their diabetes.

### COMMENT BY RALPH R. HALL, MD, FACP

It is important to note that despite a greater fall in HbA1c, the group tested with the sulfonylurea had a higher incidence of ischemic vascular disease. Thus, although the decline in HbA1c seems to be mirrored by a decline in microvascular disease, macrovascular disease may increase if there is increased weight gain and increased insulin levels.

There are not enough data at this time to indicate what the trade off is for a decrease in macrovascular disease vs. a potential for increase in microvascular disease. If one can obtain a maximum decrease in HbA1c in a segment of the population as this study suggests, it would be important to use a medication that was going to decrease the macrovascular disease as well as the microvascular disease to a minimum. Miglitol would then be an excellent choice for treating older patients whose blood glucose could be well controlled.

Previous studies have indicated that the 50 mg dose of miglitol was as effective as the 100 mg dose in reducing the blood glucose and HbA1c levels.[3] The 50 mg dose had less side effects than the 100 mg dose.

Issues that need further exploration are how adding a sulfonylurea to miglitol or miglitol to a sulfonylurea will affect the incidence of ischemic vascular disease in those patients in whom monotherapy was not adequate. The UKPDS studies showed that adding metformin to sulfonylureas in patients not responding to a sulfonylurea alone increased the incidence of macrovascular disease. This occurred despite the lowering of the incidence of macrovascular disease in patients receiving monotherapy with metformin.

The safety of other agents, such as troglitazone, continues to be questioned. Troglitazone has been withdrawn from the British market and additional cases continue to be reported in the United States.[4] It remains uncertain, as Vella and associates point out, whether adherence to the manufacturer and FDA will prevent fatal liver failure.

The use of the alpha-glucosidase inhibitors are attractive alternatives for those patients with older, mild type 2 diabetes. There also may be the potential for a decrease in macrovascular disease, as occurred in this study, since cardiovascular risk factors, such as weight gain and increased insulin resistance, do not occur. ❖

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# Update on Raynaud's: Nothing Phenomenal

ABSTRACT & COMMENTARY

***Synopsis:*** *Vasospasm, the hallmark of Raynaud's phenomenon, may have visceral as well as digital manifestations.*


**Source:** Ho M, Belch JJF. *Scand J Rheumatol* 1998;27: 319-322.


White, red, blue: the name of maurice raynaud comes to mind when cold causes fingers or toes to turn the colors of the French Tricolor. Ho and Belch have provided a brief update on Raynaud's phenomenon (RP). They stress RP as being indicative of a systemic disorder with an increased prevalence of angina and migraine, decreased renal perfusion on cold challenge, and loss of the normal increase in pulmonary diffusing capacity that

ordinarily accompanies cold exposure. On the diagnostic front, they stress the usefulness of physical findings, such as digital ulcers and pitted scars from skin ischemia, in identifying patients with systemic sclerosis (SSc). They review the characteristics of serologic tests in patients with RP and cite a 60% sensitivity and 98% specificity of anti-centromere antibodies in the limited form of SSc (CREST syndrome).[1] The anti-topoisomerase assay (anti-SCl-70) has a lower sensitivity for diffuse SSc (38%) but excellent specificity (almost 100%). The presence of anti-nuclear antibodies (ANA) increases the likelihood of progression to some connective tissue disease even if none can be diagnosed when patients first present with RP, while sero-negative patients have only a 10% progression when followed for 2-5 years.

The importance of capillary nailfold microscopy is also stressed. Loss of capillary loops or dilated loops correlates well with the presence of, or the eventual development of, some connective tissue disease.[2] Ho and Belch refer to those patients who have RP, a positive ANA, and abnormal capillary nailfold microscopy as having pre-scleroderma.

Ho and Belch review some of the evidence supporting the theory that abnormal function of the endothelium plays a major role in the pathophysiology of RP. They also note that direct vasodilators, such as nitroprusside, are less potent in subjects with RP than in normal controls, suggesting the presence of abnormalities that are independent of the endothelium.

Palliation of RP with calcium channel blocking drugs remains the mainstay of therapy, and, in Ho and Belch's opinion, nifedipine is the "gold standard." The usefulness of the prostacyclin analog, iloprost, when given intravenously in healing digital ulcers, and the disappointing lack of efficacy of of oral iloprost in patients with RP is discussed. Some promising new experimental therapies are reviewed including defibrotide, L-carnitine, and relaxin. Relaxin in particular was cited for its efficacy in digital ulcer healing in a recent trial in patients with SSc in an abstract but a peer reviewed publication has yet to appear.[3]

## COMMENT BY JERRY M. GREENE MD

The phenomenon Raynaud described 136 years ago is still with us.[4] A recent case-control study found a prevalence of RP of 5.5% based on a questionnaire and of 2.8% based on interview and examination in a population in the northern United States.[5] The normally adaptive response of decreasing peripheral blood flow in response to cold exposure is exaggerated in RP and can lead to digital infarction, ulceration, and even amputation in severely affected individuals. In addition to treating symptoms and trying to prevent the complications of Raynaud's, the other major challenge to physicians is trying to determine the prognosis for individual patients. Predicting which have a mild self-limited disorder and which have RP as a manifestation of an underlying collagen/vascular disorder is especially helpful in deciding on the frequency of follow-up and the intensity of laboratory monitoring. Patients with diffuse SSc may develop life-threatening visceral involvement early in the course of their disease. Those with limited SSc have a more protracted course but may succumb to pulmonary hypertension and associated cor pulmonale.

The usefulness of capillary nailfold microscopy in prognostication, which Ho and Belch stress, has been further supported by Spencer-Green, whose meta-analysis of 10 studies in which capillary nailfold microscopy was evaluated in a prospective fashion found that the technique had a positive predictive value of 47% (substantially better than serologic testing, which had a positive predictive value of 30%).[6] Capillary nailfold microscopy is a simple addition to the physical examination of patients with RP which can be easily performed with a hand held ophthalmoscope, a cover slip, and some immersion oil between skin and cover-slip. With the use of a +20 diopter lens, the capillary loops along the nail fold can be seen. Avascular areas (capillary drop out) or dilated capillary loops are abnormal and suggest the presence of, or eventual development of, a connective-tissue disease.

Nitroglycerin transdermal patches, which have been helpful to some patients, should be added to the list of useful treatments, though there is a high incidence of headache with this therapy.[7] Although Ho and Belch are discouraging the use of oral iloprost, investigators who conducted a recent, large multicenter, randomized controlled trial of iloprost found that either a 50 or 100 mcg dose of oral iloprost given twice daily was superior to placebo in reducing the frequency and duration (but not the number) of attacks of RP in patients with SSc.[7] Even though no phenomenal breakthroughs have occurred lately in the study of RP, some spasmodic progress continues to be made in our understanding and treatment of this colorful disorder. ❖

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## *Pharmacology Update*

# Efavirenz

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

The complexity of multidrug hiv regimens has proved to be a significant problem for HIV-infected individuals and their doctors—both in the timing of pill taking and the sheer number of pills. Now, Dupont pharmaceuticals has introduced the first once-daily anti-HIV drug. Efavirenz (Sustiva-DuPont), the third non-nucleoside reverse transcriptase inhibitor (NNRTI) on the market, was approved in September and joins nevirapine and delavirdine.

NNRTs inhibit HIV-1 activity by noncompetitive inhibition of reverse transcriptase—the enzyme responsible for the replication of the HIV virus. These antiviral agents differ in their mechanism of action from nucleoside reverse transcriptase inhibitors such as zidovudine, lamivudine, stavudine, and the newly approved abacavir, and protease inhibitors, such as indinavir, ritonavir, saquinavir, and nelfinavir.

### Indications

Efavirenz is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

### Dosing Information

The recommended dosage for adults is 600 mg once daily in combination with a protease inhibitor and/or nucleoside reverse transcriptase inhibitors. For pediatric patients (≤ 3 years of age weighing between 10 and 40 kg), the dose ranges from 200 mg to 400 mg once daily. The drug may be taken without regard to meals; however, a high-fat meal may increase the absorption of efavirenz and should be avoided.[1] Efavirenz is supplied as 50 mg, 100 mg, and 200 mg capsules. Patients should be advised to store the capsules at 77°F with excursions permitted to 59-86°F.[1]

### Potential Advantages

Efavirenz has a long elimination half-life (40-55) hours and is dosed once daily. Efavirenz with zidovudine/lamivudine (Combivir) is the most simple of the three-drug regimens (qd for efavirenz and bid for Combivir, total 5 pills per day). In a open-label trial, there were greater numbers of patients who discontinued indinavir (800 tid) + zidovudine (300 mg bid) + lamivudine (150 mg bid) due predominately to adverse events, compared to those discontinuing efavirenz (600 mg qd) + zidovudine (300 mg bid) + lamivudine (150 mg bid).[1,2] The discontinuation rates were 36.4% (56/154) and 21.6% (32/148), respectively. Efavirenz penetrates the CNS, and the concentration of efavirenz in the cerebrospinal fluid is approximately threefold that of the free (nonprotein-bound) fraction of drug in the plasma.[1]

### Potential Disadvantages

Rapid emergence of resistant HIV-1 strains, which are cross-resistant to other NNRTs, have been observed in vitro.[1] Like other NNRTs, drug interactions involving the cytochrome P450 system can be problematic. Efavirenz is both an inhibitor and inducer of CYP3A4 and an inhibitor of isoenzymes 2C9 and 2C19.[1]

Efavirenz should not be coadministered with astemizole, triazolam, midazolam, cisapride, or ergot derivatives.[1] Coadministration with indinavir would require a dose increase from 800 mg to 1000 mg every eight hours.[1] Efavirenz decreases the plasma levels of saquinavir, and, thus, the latter should not be used as a sole protease inhibitor in combination with efavirenz. INR should be monitored if warfarin is coadministered with efavirenz.

Central nervous system symptoms occur in approximately 50% of patients taking efavirenz.[1] These symptoms include dizziness, impaired concentration, delusions, depression, and/or drowsiness.[1] Patients should be warned about potential additive effects with other CNS depressants and cautioned against driving and operating machinery if patients experience these symptoms. As with other NNRTs, rash has been reported. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks after initiation of therapy (median time, 11 days). Rash associated with blistering, moist desquamation, or ulceration occurred in 1% of adult patients (n = 455) compared to 3.5% in children (n = 57). The incidence of serious rash (e.g., erythemia multiforme, Steven-Johnson Syndrome, toxic epidermal necrolyis) was reported in 3.5% of children taking efavirenz.[1] In general, rash was more common and of greater severity in children.[1] Due to potential for fetal damage, efavirenz should be avoided in pregnant women.[1]

### Comments

The FDA approved Efavirenz in September after a two month review. Similar to other agents, approval was

based on changes in HIV-RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. The primary end point was the percent of patients with plasma HIV-RNA less than 400 copies/mL using the Roche RT-PCR HIV-1 assay.[1] Study details are only available in abstract form, review article, or provided in the product information.[1,2,3,7,8] These suggest that efavirenz in combination with zidovudine and lamivudine was at least as effective as indinavir with zidovudine and lamivudine or efavirenz and indinavir in antiretrovial naive patients (n = 450).[1,2] These patients had an average CD4 cell count of 345 cells/$mm^3$ and a mean HIV-RNA plasma level of 4.77 $\log^{10}$ copies/mL. The higher discontinuation rate of the protease inhibitor three-drug combination actually made the efavirenz three-drug combination appear more effective based on intent-to-treat analysis.[7] At 36 weeks, the results favored the efavirenz combination with 66% of the patients achieving RNA less than 50 copies/mL (using ultrasensitive assay) compared to 50% for the indinavir regimen.[7,8] The addition of efavirenz to a three-drug combination was reported to be more effective than a three-drug combination (indinavir + 2 NRTIs) in NRTI experienced but PI and NNRTI-naïve patients (mean RNA baseline copies > 4.39 $\log^{10}$ copies/mL).[3] At 24 weeks, viral load reductions were 2.3 $\log^{10}$ and 1.6 $\log^{10}$ and 54% and 37% with RNA less than 50 copies/mL, respectively.[3,8] As with all previous antiretroviral agents, emergence of resistance can be rapid with monotherapy. Also similar with other NNRTs, drug interaction and rash can be problematic. Long-term effectiveness and safety of efavirenz remain to be determined. Efavirenz is priced similar to the protease inhibitors, at $329 per month.

### Clinical Implications

Efavirenz offers another alternative antiretroviral agent for the management of HIV-1 infection. There does not appear to be cross resistance between efavirenz and protease inhibitors. Zidovudine-resistant strains derived clinically have retained susceptibility to efavirenz.[1] As with other antiretroviral agents, monotherapy with efavirenz promotes the rapid emergence of resistant virus. Efavirenz must be used in combination with other agents and should not be added as a sole agent to a failing regimen.

The Department of Health and Human Services, The International AIDS Society, and The British HIV Association published guidelines for antiretrovial therapy in 1998.[4,5,6] The current standard is to initiate therapy with one or two protease inhibitors with two NRTIs. The weight of the clinical data supports a regimen of a protease inhibitor with two NRTIs. NNRTIs, such as efavirenz, offer a potential alternative to a protease inhibitor. These can be used with two NRTIs with or without a protease inhibitor. Recently, the Department of Health and Human Services updated their earlier guidelines and considered efavirenz the preferred NNRTI, citing its comparable viral suppression activity to indinavir.[9] The initial antiretrovial regimen is no doubt the most critical one for the course of the disease. Factors to consider when initiating therapy are viral load, CD4 cells, potential drug toxicities, drug interactions, and the patient's willingness to commit to adhering to the complex drug regimens. Efavirenz's once-daily dosing may offer an advantage over other antiretrovirals in reducing regimen complexity. Early initiation of treatment appears to be associated with virologic, immunologic, and clinical benefit.[4] Treatment should be supervised by an expert in HIV therapy. ❖

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## CME Questions

**5. Which of the following statements is *not* true?**

a. Alpha-glucosidase inhibitors act by reducing post-pryandial blood glucose rises.
b. Hypoglycemia is a frequent problem with alpha-glucosidase inhibitors.
c. In the study by Johnston et al, there was a decrease in cardiovascular events in patients taking migitol.
d. The UKPDS studies, as well as the DCCT studies, show that the incidence of microvascular disease decreases as the HbA1c is lowered.

**6. Which of the following is the most specific for the limited form of systemic sclerosis (CREST syndrome)?**

a. Antibodies to topoisomerase (SCl-70)
b. Abnormal capillary nailfold microscopy
c. Antibodies to centromeres
d. Sclerodactly

By Louis Kuritzky, MD

## A New Dipstick Test for Microalbuminuria Screening in Patients with Hypertension

Increased urinary excretion of protein is a marker for future development of cardiovascular disease among hypertensive patients and correlates with the risk of mortality in diabetics. Traditional office testing materials for albumin requires at least 300-500 mg/d albumin excretion to indicate a positive test; since much lower levels of urinary albumin excretion (UAE) are abnormal (normal is < 30 mg/d), there has been a window wherein abnormal UAE may be missed in typical outpatient practice, unless the clinician resorts to the somewhat cumbersome and expensive 24-hour urine analysis.

In diabetics, interventions addressed at improving microalbuminuria with ACE inhibitors have shown less progression to overt nephropathy. Hence, it has been felt that early detection of even modest levels of UAE above normal is desirable. For this purpose, the Micral-Test (Boehringer Manheim, Indianapolis, IN) has been developed. The current study is the first to evaluate its efficacy in hypertensive patients.

In a patient population of 171 hypertensives, Micral-Test was compared with 24-hour urine collection. The sensitivity of random urine sampling was 92%. Equally valuable as the high sensitivity, Gerber and colleagues acknowledge a very small (≤ 5%) false-positive rate. Gerber et al conclude that Micral-Test is a valuable screening tool for microalbuminuria. ❖

*Gerber LM, et al. Am J Hypertens 1998;11:1321-1327.*

## Generalist and Pulmonologist Care for Patients Hospitalized with Severe COPD

Copd is the fourth leading cause of death in the United States. Comparison of generalist with specialist care of COPD has focused on ambulatory settings, but much of the cost of COPD and mortality is located in hospital settings. The current study is the first to specifically compare the care of these two professional groups in reference to inpatient COPD management.

Five academic medical centers enrolled 866 adults with severe COPD. The Therapeutic Intervention Scoring System score was used to assess intervention use on days 1, 3, 7, 14, and 25 of patient care; this system scores minor interventions like an IV or pulse oximetry 1 point, and 2-4 points for greater intensity interventions, such as arterial lines, intubation, or surgical procedures. Additionally, expenses were recorded from hospital billing records.

Both adjusted average resource intensity scores and estimated hospital costs were the same for patients treated by pulmonologists as those treated by generalists. Regueiro and associates conclude there is not a significant difference in resource use, cost, or survival of COPD patients between pulmonologists and generalists. ❖

*Regueiro CR, et al. Am J Med 1998; 105:366-372.*

## Mortality Results for Early Elective Surgery or Ultrasonographic Surveillance for Small Abdominal Aortic Aneurysms

Although elective repair of large abdominal aortic aneurysms (AAA) reduces mortality, small aneurysms are often followed by observation with repeat ultrasonographic measurement. Unheralded rupture of an AAA is always associated with a high mortality rate, hence, the potential for elective early intervention is theoretically attractive. This study compared, in patients older than 60 years (n = 1090), elective surgical repair of small AAA (4.0-5.5 cm) vs. ultrasonographic surveillance for 4-6 years. Ultrasound was performed every six months for AAA 4.0-4.9 cm, and every three months for AAA 5.0-5.5. Additionally, if growth rate was greater than 1 cm/yr or if AAA became tender or symptomatic, surgery was offered to the patient. Statistical analysis of overall mortality by intention-to-treat methodology was performed.

In the first 30 days of the trial, the 5.8% mortality rate seen in the surgical group provided a statistical disadvantage. At all end point times, the surgical group enjoyed no advantage over ultrasonographic surveillance. The authors conclude that early surgical intervention is not advantageous over ultrasonographic surveillance in terms of mortality for AAA less than 5.5 cm. ❖

*The UK Small Aneurysm Trial Participants Lancet 1998;352:1649-1655.*

## In Future Issues:

Gleason Scores of Localized Prostate Cancer Predict the Risk of Dying from Prostate Cancer

Nephrolithiasis and the Risk of Hypertension in Women