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## Something to Offer Your Fibromyalgia Patients

ABSTRACT & COMMENTARY

**Synopsis:** Most women with fibromyalgia have a variant of sleep apnea when carefully tested, and their symptoms improve with CPAP treatment.

**Source:** Gold AR, et al. *Sleep*. 2004;27:459-466.

**G**OLD AND COLLEAGUES HYPOTHESIZED THAT DISRUPTED SLEEP resulting from excessive work of breathing while asleep may contribute to the symptoms of fatigue, bodily pain, heartburn, depression, and insomnia frequently reported by fibromyalgia patients. To evaluate this, they assessed the amount of inspiratory work (negative pressure, or suction) and the amount continuous positive airway pressure (CPAP) necessary to overcome additional work in patients with fibromyalgia and the Upper Airways Resistance Syndrome (UARS), which is believed to be a variant of obstructive sleep apnea. In brief, inspiratory airflow limitation (and excessive work of breathing) is present when an individual continues to try to inhale (generates negative intrathoracic pressure) but cannot move air. With normal breathing, of course, negative intrathoracic pressure generates inspiratory airflow. With sleep-disordered breathing such as sleep apnea or UARS, increasingly negative (stronger) inspiratory pressures (eg, suction) are needed to generate flow, and ultimately cannot produce flow (resulting in frank apnea). To assess inspiratory airflow limitation, airflow is measured with a pneumotachograph, and negative intrathoracic pressure is measured with an esophageal pressure catheter. Gold and colleagues attempted to determine if inspiratory airflow limitation were present by measuring the pressure (suction level) at which the upper airway closed off (Pcrit) during non Rapid Eye Movement (NREM) sleep, and also by measuring how much positive airway pressure it took to provide unrestricted inspiratory airflow during inspiratory efforts.

The study population consisted of 28 fibromyalgia patients and 11 patients with UARS. Fibromyalgia was diagnosed by a rheumatologist in every case. All patients were women. Their average age was mid-40s, and their average Body Mass Index (BMI) was 29 Kg/m<sup>2</sup>. Half of the FM patients did not snore reg-

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VOLUME 26 • NUMBER 10 • MAY 29, 2004 • PAGES 73-80

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ularly, and 10 did not snore at all.

In this study, 27 of the 28 patients with fibromyalgia had inspiratory airflow limitation during NREM sleep. 26 had UARS, one had sleep apnea, and only one had no flow limitation. In this group of patients, 90% of their breaths were flow-limited, with an average change in intrathoracic pressure (suction) of -13 cm H<sub>2</sub>O (normal is -2 to -4 cm H<sub>2</sub>O). It took an average of 7 cm H<sub>2</sub>O CPAP to eliminate the flow limitation. Arousals from sleep associated with episodes of airway obstruction resulted in alpha intrusion, or alpha delta sleep, the characteristic sleep EEG pattern of patients with fibromyalgia. Very similar findings were seen in the UARS patients. Only one of the fibromyalgia patients did not have inspiratory flow limitation. She did not differ from the other patients

in any other way.

Fourteen of the fibromyalgia patients accepted CPAP treatment for sleep-disordered breathing. For this group, there was a 46% improvement in fatigue, and 30% improvement in pain, a 39% improvement in sleep problems, a 23% decrease in functional disability, a 33% decrease in the rheumatology distress index, and a 47% improvement in GI symptoms after 3 weeks of CPAP treatment. 5 of the subjects chose to remain on CPAP after the trial.

#### ■ COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

As internists, we regularly encounter patients who have been diagnosed with or who think they may have fibromyalgia. As a sleep specialist, I frequently encounter these patients, often referred to evaluate the possibility of sleep apnea, but sometimes simply sent in a desperate attempt to explain poor sleep quality and daytime fatigue. This paper suggests that many patients with fibromyalgia have respiratory pathophysiology like that of sleep apneics. In fact, they appeared to be very similar to patients with UARS, which has been thought to be a sleep apnea variant. Since the original description of UARS by Guilleminault,<sup>1</sup> sleep specialists have believed that subtle obstructed breathing events could cause some of the symptoms of obstructive sleep apnea (OSA), and that this could account for many of the symptoms seen in the so-called functional somatic syndromes, notably fatigue and body pain. An interesting finding of this paper is that the pattern of alpha-delta sleep was seen in these patients related to arousals resulting from inspiratory airflow resistance.

I discussed these findings with the study's author, Ave (rhymes with Dave) Gold. I told him I was impressed that he had chosen to work with the fibromyalgia population, which can be difficult. His reply:

"I did my best to ignore their fibromyalgia. I was just interested in treating their UARS. But then one of my referrals came in and told me she was referred by a friend in her FM support group because I had 'cured' her friend's FM. I have studied at least 45 FM patients already and I am still looking for my second without flow limitation. The same is true for all the functional somatic syndrome patients that I have seen clinically. Moreover, if you can treat their SDB (sleep-disordered breathing), you can greatly improve (not cure) their functional symptoms. If you look at the FSS (Functional Somatic Syndrome) literature, however, they do not have a clue. Rheumatologists, Neurologists, GI's do not emphasize sleep as a cause of the FSS. In short, sleep apnea is the tip of the iceberg when it comes to the clini-

*Internal Medicine Alert*, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road, NE, Building 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Internal*

*Medicine Alert*, P.O. Box 740059, Atlanta, GA 30374.

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*Internal Medicine Alert* has been approved by the American Academy of Family Physicians as having educational content acceptable for prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of January 1, 2004. This volume has been approved for up to 45 prescribed credit hours. Credit may be claimed for one year from the date of this issue.

The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours. This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

#### Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Brunton is a consultant for Andrax, Reliant, and AstraZeneca and serves on the speaker's bureau of Janssen, Schering, Aventis and AstraZeneca. Dr. Hall is a consultant for Aventis. Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3-M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. Dr. Ost is on the speaker's bureau of Merck, Roche, and Boehringer Ingelheim and does research for the American Lung Association. Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Merck, Res Med, and GlaxoSmithKline and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and Res Med. Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca, and Centocor. Drs. Chan, Elliott, Grauer, Karpman, Wiese, and Wilke report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

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cal effects of SDB. This has become my ‘mission’—doing the work that is needed to enable patients with FSS to get real help. With that, I will get off my soap box! Also . . . FSS patients are not that hard to deal with *if you have something to offer.*”

*Wow! This has the potential to change my practice. It’s important to remember that patients can have inspiratory flow limitation and sleep disturbance as a result without having snoring or typical symptoms and signs of sleep apnea. It’s even more important to remember that we may have something to offer these patients!* ■

## Can You Spell “El Mundo” Backwards?

ABSTRACT & COMMENTARY

**Synopsis:** *When administering the MMSE, use of serial 7s produces a more reliable score.*

**Source:** Espino DV, et al. *J Am Geriatr Soc.* 2004;52:822-827.

THE SAN ANTONIO LONGITUDINAL STUDY OF AGING (SALSA) enrolled Mexican-American (MA) and European-American (EA) elders from 3 distinct neighborhoods that were predominantly low-, middle-, and upper-income. The neighborhoods had varying mixes of MA and EA with the low-income one being almost exclusively MA, the middle-income one an even split, and the upper-income one 90% EA. All subjects were given the Mini-Mental State Examination (MMSE) with 2 modifications: all were asked to spell “WORLD” backwards and in performing the 3-step command (“Take this paper in your right hand, fold it in half, and place it on the floor.”), they were instructed to place the paper on their lap. The MMSE was scored 3 different ways: taking the better score of serial 7s or backwards spelling, serial 7s alone, and backwards spelling alone.

The subjects fell into 3 groups: EA, MA who were interviewed in English (MAE), and MA who were interviewed in Spanish (MAS). There were 807 subjects (363 EA, 320 MAE, and 124 MAS), averaging 69 years in age and predominantly female (58%). The 3 groups differed in educational achievement with EA having completed high school and some college, MAE having completed some high school, and MAS having completed some grade school. Most (80%) of the MAS lived in the low-income neighborhood; only 47% of MAE lived there. EA rated their health better than MA. This was

borne out when comparing the incidence of diabetes mellitus, type 2: 12% EA, 30% MAE, and 50% MAS.

The scores on the MMSE by ethnic group and method of scoring were as follows:

Scoring methods Mean ± SD	EA	MAE	MAS
Spelling or serial 7s	28.5 ± 1.9	26.9 ± 3.0	23.6 ± 4.8
Serial 7s only	27.7 ± 2.4	25.6 ± 3.2	22.3 ± 4.5
Spelling only	28.5 ± 1.7	27.2 ± 2.6	25.5 ± 3.5

The coefficients of variation (a measure of heterogeneity) were lowest for EA and highest for MAS with MAE in the middle. The serial 7s only scores had greater variability than spelling or serial 7s and spelling only. The serial 7s only scores also had the highest alpha coefficients, a desirable trait for screening tests.

### ■ COMMENT BY ALLAN J. WILKE, MD

The MMSE celebrates its 30th birthday next year. As Dr. Marshall Folstein has noted, “age and education produce remarkably similar results across cultures.” In the same article he notes that there is ambiguity in scoring serial 7s and that serial 7s and spelling “world” backwards are not comparable. His personal practice is to use spelling only if “the patient absolutely refuses to try” serial 7s. ■

## Exercise Training for Angina

ABSTRACT & COMMENTARY

**Synopsis:** *A 12-month program of regular exercise in selected patients with chronic stable angina and significant CAD resulted in a higher event-free survival and exercise capacity at lower costs than PCI.*

**Source:** Hambrecht R, et al. *Circulation.* 2004;109:1371-1378.

ALTHOUGH PERCUTANEOUS CORONARY INTERVENTIONS (PCI) are highly efficacious in acute coronary syndromes, their benefit in chronic stable exercise-induced angina is less clear. Thus, Hambrecht and associates from Leipzig, Germany, randomized 101 men with class I-III angina younger than 70 years of age to 20 minutes of exercise per day or PCI after routine coronary angiography showed significant coronary artery disease (CAD). Exclusion criteria included negative stress tests for ischemia, recent myocardial infar-

tion, left main or proximal left anterior descending disease, ejection fraction < 40%, and insulin-dependent diabetes. Over 12 months, exercise training exhibited a higher event-free survival as compared to PCI (88 vs 70%;  $P = .023$ ). The difference in events was mainly due to rehospitalizations for ischemic events and revascularization. There were no deaths. Repeat angiography showed that 32% of exercise patients had CAD progression vs 45% of the PCI patients ( $P = .035$ ). Significant improvements in stress myocardial perfusion were observed in both groups, but the increase in exercise oxygen consumption was greater in the exercise group (16% vs 2%;  $P < .001$ ). The cost needed to gain one angina class was \$3,429 in the exercise group vs \$6,956 in the PCI group ( $P < .001$ ). Hambrecht et al concluded that a 12-month program of regular exercise in selected patients with chronic stable angina and significant CAD resulted in a higher event-free survival and exercise capacity at lower costs than PCI.

#### ■ COMMENT BY MICHAEL H. CRAWFORD, MD

Previous single-center experience has shown increased survival and exercise tolerance in CAD patients treated with exercise training, but no randomized trials have been done. For that reason, this trial is of interest. It generally agrees with other medical vs revascularization trials, and it is not surprising that exercise training increased exercise tolerance more than PCI, since most CAD patients are sedentary despite our advice to exercise. Interestingly, both groups experienced a reduction in angina, which is consistent with other studies of revascularization, but less well established for exercise training. Since coronary lesion regression was not seen with exercise training, the mechanism of this benefit is unclear but may be due to improved vasomotor tone. That the reduced total direct costs were less in the exercise-training group is not surprising because of the cost of the initial PCI. However, the decrease in subsequent hospitalizations and procedures in the exercise group is less expected. This suggests that in such low-risk patients, the complications of PCI end up negating its benefits as compared to conservative therapy. Of course, drug-eluting stents were not used. Perhaps they would have significantly reduced the 15% restenosis rate observed in the PCI group and altered the conclusions of this study. Also, this is a small trial, so the conclusions must be tempered. In addition, these were very low-risk patients as evidenced by the zero death rate. Thus, the major implication of this small, randomized trial is that medical therapy with exercise training is a viable alternative to PCI in low-risk patients with chronic

stable angina due to CAD. Of course, only selected patients will be able to adhere to this consistent exercise program, but for those who are motivated, exercise training plus maximal medical therapy may be highly effective. The COURAGE trial is testing the hypothesis that maximal medical therapy plus PCI will be better for patients with CAD than maximal medical therapy alone, but this trial does not include formal exercise training. I believe American physicians have given up on getting Americans, especially women, to exercise regularly. Perhaps this approach will only work in Europe and other places where regular exercise is more accepted. It is interesting to speculate on what PCI, maximal medical therapy, and exercise could do. ■

*Dr. Crawford is Professor of Medicine, Associate Chief of Cardiology for Clinical Programs, University of California, San Francisco.*

## Rate Control in Atrial Fibrillation—Why? How?

ABSTRACT & COMMENTARY

**Synopsis:** Management of atrial fibrillation with a rhythm-control strategy conferred no advantage over a rate-control strategy in cardiac or vascular mortality and may be associated with an increased noncardiovascular death rate.

**Source:** Steinberg JS, et al and the AFFIRM Investigators. *Circulation*. 2004;109:1973-1980.

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION of Rhythm Management (AFFIRM) Study was a large, multicenter, randomized trial sponsored by the National Heart, Lung, and Blood Institute. The study compared rate-control vs rhythm-control therapy in the treatment of atrial fibrillation (AF) in a population at high risk of stroke or death and found that rate control was an acceptable, if not a preferable, option.<sup>1</sup> Several sub-studies have been generated from the AFFIRM data; for example, one recent study revealed that management of AF with a rhythm-control strategy conferred no advantage over the rate-control strategy with respect to cardiac or vascular mortality and, in fact, the rhythm-control approach may actually be associated with an increase in the noncardiovascular death rate.<sup>2</sup>

Brian Olshansky and the AFFIRM investigators rean-

alyzed the AFFIRM data focusing and then comparing the effects of several drug classes with respect to their ability to control the ventricular rate in patients with AF.<sup>3</sup> Adequate rate control was defined as an initial resting heartrate equal to or less than 80 beats/minute and a Holter monitor recording which demonstrated an average heartrate equal to or less than 100 beats/minute and no heartrate over 110% maximum predicted age-adjusted exercise heartrate or with a standard 6 minute walk test during which the maximum heart rate was equal to or less than 110 beats/minute.<sup>4</sup> Drug categories included beta-blockers, calcium channel blockers and digoxin, alone or in combination. Beta-blockers proved to be the most effective of the 3 drug classes and, in fact, overall rate control was achieved in 70% of patients given beta-blockers as the first drug with or without digoxin. By comparison, calcium channel blockers with or without digoxin achieved an overall rate control in only 54% of patients. It should be noted that adequate rate control was achieved in all patients although frequent medication changes and/or drug combinations were needed to achieve this result.

#### ■ COMMENT BY HAROLD L. KARPMAN, MD

Ventricular rate control in patients with AF improves symptoms, exercise capacity, and cardiac function.<sup>5-10</sup> However, rate control is often difficult to achieve as was demonstrated in the AFFIRM study in which the therapeutic regimen had to be changed at least once in approximately one third of patients.<sup>3</sup> In that study, digoxin was often used successfully both as a single drug and in combination with other drug classes without undue risk. Verapamil alone or in combination with digoxin was found to be superior to digoxin alone. Also, calcium channel blockers were found to be less effective than beta-blockers both at rest and with exertion and, more patients were switched from calcium channel blockers to beta-blockers than vice versa. Since adequate rate control was frequently not easy to achieve, medication changes and/or combinations of drugs were often necessary in order to slow the ventricular rate in patients with AF.<sup>3</sup> However, most patients eventually had an adequate response to one or a combination of the available drug classes. Beta-blockers tended to be used more commonly over time and fewer patients abandoned this drug class when compared to calcium channel blockers and digoxin.

Finally, it should be clearly recognized that scientifically valid outcome data demonstrating that heart rate control in patients with AF result in longer lives, fewer hospitalizations or improved quality-of-life is not available at this time. However, until new drugs and proven

outcome data are available, it seems both logical and reasonable to pursue rate control aggressively in patients with AF at this time and this approach is reflected in current cardiology guidelines which should be carefully followed.<sup>11</sup> ■

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## Pharmacology Update

### Telithromycin Tablets (Ketek)

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

THE FDA HAS APPROVED TELITHROMYCIN, THE FIRST ketolide antibiotic. Ketolides are semisynthetic derivatives of the macrolide erythromycin that have activity against a wide spectrum of respiratory bacterial pathogens including multi-drug resistant *Streptococcus pneumoniae*. Telithromycin, which is a once a day oral tablet, is marketed by Aventis as Ketek.

#### Indications

Telithromycin is approved for the treatment of acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus*

*influenzae*, or *Moraxella catarrhalis*; acute bacterial sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*; and community acquired pneumoniae (CAP) of mild to moderate severity caused by *Streptococcus pneumoniae* (including multi-drug resistant isolates), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, or *Mycoplasma pneumoniae*.<sup>1</sup>

### Dosage

The recommended dose for acute bacterial exacerbation of chronic bronchitis or acute bacterial sinusitis is 800 mg once daily for 5 days. The recommended dose for community-acquired pneumonia of mild-to-moderate severity is 800 mg once daily for 7 to 10 days. Telithromycin can be taken with or without food.<sup>1</sup>

Telithromycin is supplied as 400 mg tablets.

### Potential Advantages

Telithromycin has shown in-vitro activity and clinical efficacy against multi-drug resistant *S pneumoniae*.<sup>1-6</sup> It also appears to have low potential to select for or induce macrolide lincosamide streptogramin B (MLSb) resistance.

### Potential Disadvantages

The most common side effects were diarrhea (13.3%) and nausea (8.1%). Telithromycin is a substrate and inhibitor of CYP 3A4. Potent inhibitors increase the bioavailability of telithromycin, and the bioavailability of certain substrates of CYP 3A4 (eg, simvastatin, midazolam) are increased. Telithromycin has the potential to prolong QTc and should be avoided in patients at risk. Exacerbations of myasthenia gravis and visual disturbances (eg, blurred vision, diplopia, problems with accommodation) have been reported.<sup>1</sup> Strains of *S pneumoniae* resistant to telithromycin have been demonstrated in vitro.<sup>1</sup>

### Comments

Telithromycin, while derived from erythromycin, has higher binding affinity to ribosomes than erythromycin. It is active with dose dependent bactericidal activity against common respiratory bacterial pathogens including atypical/intracellular pathogens and drug resistant strains of *S pneumoniae*. Concentrations exceeding the MIC90 are achieved in bronchial mucosa and epithelial lining fluid.<sup>7</sup> Clinical cure rates of telithromycin (800 mg daily) were com-

parable to comparators such as clarithromycin (1000 mg daily), trovafloxacin (200 mg daily), and amoxicillin (3000 mg daily) for community acquired pneumonia; amoxicillin/clavulanate (1500/375 mg daily) and cefuroxime axetil (500 mg daily) for acute bacterial sinusitis; and cefuroxime, amoxicillin/clavulanate, and clarithromycin for acute exacerbation of chronic bronchitis.<sup>1,2</sup> Clinical cure has also been reported in a limited number of infections caused by multi-drug resistant *S pneumoniae*. These include isolates resistant to 2 or more of the following: penicillin, 2nd generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.<sup>1</sup> Overall clinical cure ranged from 85-91% in these resistant pathogens.<sup>1,2</sup> Bacterial eradication of erythromycin or penicillin resistant *S pneumoniae* in CAP was 92% (67/73) for telithromycin compared to 70% (7/10) for pooled comparators.<sup>2</sup> Telithromycin is generally well tolerated with diarrhea and nausea as the most common side effects. Exacerbations of myasthenia gravis and visual disturbances have been reported. The cost of telithromycin was not available at the time of this review.

### Clinical Implications

Epidemiologic data indicate that bacterial resistance to commonly used antibiotics such as penicillin and erythromycin is increasing.<sup>8</sup> Penicillin resistant *S pneumoniae* represents over half the isolates in many regions of the United States, erythromycin-resistant strains ranges from 23-41%, and penicillin and erythromycin resistance ranges from 13-30%. Telithromycin appears to be an effective antibiotic for these resistant bacteria. It must, however, be prescribed judiciously to minimize development of bacterial resistance as resistant strains have been demonstrated in vitro. ■

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## CME Questions

26. When administering the Mini-Mental State Exam, use of which of the following yields the best discrimination between patients of varying mental acuity?

- serial 7s score only
- spelling score only
- the better score of spelling and serial 7s
- administering the test in Spanish
- none of the above

27. Fibromyalgia patients:

- Often have inspiratory airflow limitation during sleep.
- Are less compliant with CPAP than are other patients.
- Do not generally respond to nonpharmacologic treatment.
- Are not frequently encountered in Internal Medicine practices.
- Are typically below ideal body weight.

Answers: 26 (a); 27 (a)

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By Louis Kuritzky, MD

## Alendronate for Osteoporosis

THE BISPHOSPHONATES ALENDRONATE (ALE) and risedronate are the most commonly used pharmacologic agents for the treatment and prevention of osteoporosis (OSPS). Bisphosphonates have been shown to reduce fracture rates and improve bone mass, but previous studies have been limited to windows of observation no longer than 5 years. Because patients may be receiving bisphosphonates for decades, longer-term studies are of great value.

The study population reported by Bone and colleagues included women (n = 247) from an original study group of 994 who were randomized to a placebo-controlled 3-year study of ALE. At the conclusion of that study, women were invited to extend treatment with ALE 5 or 10 mg/d for an additional 2-7 years. Some of the women who had been originally assigned to ALE were given placebo, which also allowed determination of whether bone accrual effects would recede upon discontinuation of treatment.

Both ALE doses provided increases in bone density over 10 years, maximally in the lumbar spine (13.7% increase) and least in the femoral neck (5.4% increase). The nonvertebral fracture rate during the years 6-10 of the study was similar to that seen in the first 3 years, in which there were approximately 20% fewer fractures in the ALE group. Bone markers indicated that ALE benefits gradually diminished upon discontinuation. ALE is well tolerated and maintains efficacy with long-term administration. ■

Bone HG, et al. *N Engl J Med.* 2004;350:1189-1199.

## Exercise Training in Patients Chronic Heart Failure

IN THE NOT TOO-DISTANT PAST, CLINICIANS were apprehensive about exercise for patients with chronic heart failure (CHF). Evolution of knowledge about optimizing treatment in CHF has recognized that exercise may indeed provide symptomatic benefits. The effect of exercise upon mortality has not been examined, or study populations have been too small to derive meaningful data. By meta-analysis, data from 9 studies (n = 801) provides a sturdier picture of the impact of exercise upon mortality.

In the studies used to comprise the meta-analysis group, exercise programs attained peak oxygen consumption intensity ranging from 50-80%, by means of cycling, walking, or other aerobic activities. All programs provided supervised activity, ranging from 30-60 minutes per day on multiple days per week. Followup was up to approximately 2 years. To ensure that effects were related to exercise, and not changes in pharmacotherapy, drug regimens were examined. No changes in ACE inhibitors, beta blockers, or antialdosterone agents occurred during exercise study periods.

Exercise provided a favorable 35% risk reduction in mortality and 28% reduction in the combined end point of death or hospitalization. The optimum intensity, duration, method, and frequency of exercise remain unknown, but clinicians should be encouraged that aerobic exercise may be life-prolonging in patients with CHF. ■

ExTraMATCH Collaborative. *BMJ USA* 2004;4:109-112.

## Cardiovascular Prognosis of "Masked Hypertension"

THERE IS CONSISTENT AGREEMENT that ambulatory blood pressure monitoring (ABPM) provides a better indicator of ultimate cardiovascular risk than office blood pressure (OBP). Because measurement of BP at home (HBP) often frees the patient from stressors which could lead to spuriously elevated BP (white coat HTN), we are sometimes aided by such measurements in directing treatment. Unfortunately, trial data based upon HBP measurement is sparse.

The Self Measurement of BP at Home in the Elderly study followed almost 5,000 participants for 3 years. Subjects had BP measured in the office after a 5-minute rest. At home, patients measured BP 3 times each morning and evening.

During followup, 205 deaths occurred (85 cardiovascular). HBP was predictive of cardiovascular events in men and women, for both systolic and diastolic BP. There was a small group of individuals (9% of total group) whose BP was elevated on HBP measurement, but *not* in the office. These individuals also reflected an increased cardiovascular risk. Bobrie and associates conclude that HBP measurement is a better prognostically than office BP. Indeed, they have identified a heretofore little-described population known as 'masked hypertension', who have elevated blood pressures at home despite normal office BP. ■

Bobrie G, et al. *JAMA.* 2004;291:1342-1349.