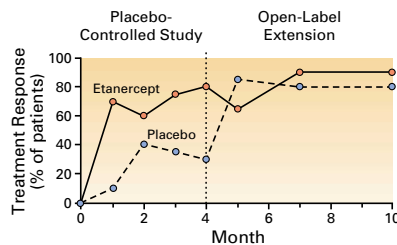




# This Week in the Journal

May 2, 2002

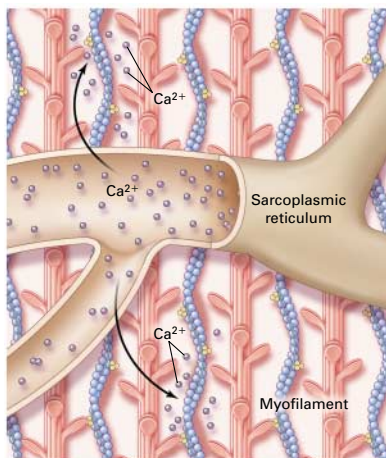
## Treatment of Ankylosing Spondylitis by Inhibition of Tumor Necrosis Factor $\alpha$



Ankylosing spondylitis is difficult to treat — those affected often have acute inflammation and discomfort even decades after the onset of the disease. Since tumor necrosis factor  $\alpha$  appears to have a role in spondyloarthritides, the authors used etanercept, a recombinant human tumor necrosis factor receptor:Fc fusion protein, in a randomized, placebo-controlled trial followed by an open-label extension study. Treatment with etanercept resulted in significant and sustained improvement; at four months, 80 percent of the patients treated with etanercept had reached the primary end point, a treatment response, as compared with 30 percent of the placebo group. The patients who initially received placebo had rapid improvement during the six-month extension study, when both groups received etanercept.

*The results of this study support the concept that inhibition of tumor necrosis factor  $\alpha$  leads to clinical improvement in patients with ankylosing spondylitis. The long-term outcome of such treatment is not known.*

see page 1349 (editorial, page 1399)



## Myocardial Gene Expression in Dilated Cardiomyopathy

Beta-blocker therapy may benefit patients with dilated cardiomyopathy. In this study, the expression of myocardial genes affecting cardiac contractility and hypertrophy was studied before and after the initiation of beta-blocker therapy. A response to therapy was accompanied by increased expression of genes such as those encoding  $\alpha$ -myosin heavy chain and calcium ATPase in the sarcoplasmic reticulum.

*Effective therapy for heart failure, in this case with beta-blockers, is accompanied by changes in the expression of key myocardial genes that are involved in the regulation of cardiac contractility.*

see page 1357 (Perspective, page 1346)

## PERSPECTIVE

## Beta-Blockers for Stable Heart Failure

According to current recommendations,  $\beta$ -adrenergic-receptor blocking agents should be prescribed for all patients who have symptomatic heart failure and are in stable condition, unless these agents are contraindicated. The impetus for this approach is often traced to Göteborg, Sweden, where Waagstein and colleagues observed that the administration of  $\beta$ -adrenergic-receptor blocking agents decreased pulmonary congestion in some patients with acute myocardial infarction and elevated heart rate. Speculating that “patients with congestive heart failure from other causes might also respond well to a reduction of tachycardia by beta-adrenergic receptor blockade,” in 1975 they reported successful use of beta-blocking agents with partial intrinsic sympathomimetic activity, with a decrease in the average heart rate from 98 to 79 beats per minute within a week. Although a reduction in heart rate remains a predictor of benefit from beta-blockade, many neurohormonal and hemodynamic effects of reduced sympathetic stimulation also contribute. The left ventricular ejection fraction increases within three to six months after the start of therapy in most patients. The report by Lowes et al. in this issue of the *Journal* (pages 1357–1365) demonstrates an association between improvement in clinical function and normalization of myocardial gene expression, providing further rationale for the use of beta-blockers.

In an initial randomized trial in 383 patients with heart failure, metoprolol tartrate did not improve survival, but since then multiple randomized trials of beta-blockers,

involving more than 15,000 patients, have demonstrated a cumulative relative reduction of 30 to 40 percent in both mortality and morbidity. The observed benefits translate into the prevention of 3 to 4 deaths during the first year of therapy for every 100 patients treated with a beta-blocker for mild-to-moderate heart failure.

### Who Are the Patients?

Trials have focused on patients with mild-to-moderate heart failure (New York Heart Association class II or III) (see Figure). Beta-blockers are also recommended for asymptomatic patients after myocardial infarction, but current guidelines do not address their use in patients who have asymptomatic left ventricular dysfunction without coronary artery disease. The main contraindications are bronchospasm and bradycardia. As expected, when a compensatory reflex response is interrupted, hemodynamic decompensation can be aggravated by beta-blocker therapy, with increased filling pressures and decreased cardiac output. Initiation of beta-blocker therapy is thus not recommended in patients with no hemodynamic reserve, as indicated by obvious fluid retention, symptoms of congestive failure at rest, or recent hospitalization for intravenous vasoactive therapy. Such patients with severe symptoms have been consistently excluded from trials, but they are candidates for beta-blocker initiation if their condition can be stabilized with oral medications to a profile of heart failure without congestion. Beta-blocker therapy can usually be maintained in patients who present with symptoms of fluid retention after a period of stability during beta-blocker therapy, as long as they do not have evidence of low cardiac output.

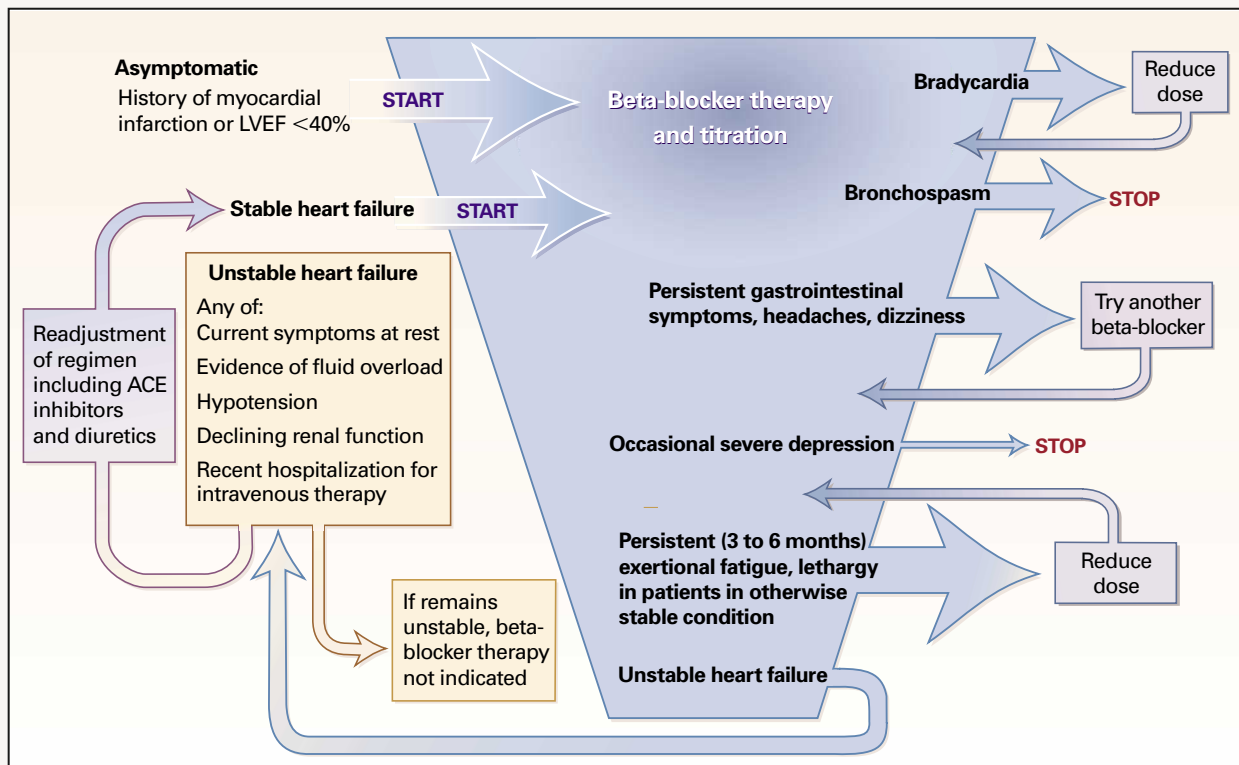
### Which Beta-Blockers?

Benefit has been shown with beta-blocking agents that selectively inhibit  $\beta_1$  receptors, such as

metoprolol or bisoprolol, and with those that inhibit both  $\beta_1$  and  $\beta_2$  receptors, such as carvedilol, with or without peripheral vasodilatation. Carvedilol causes vasodilatation through blockade of  $\alpha$ -adrenergic receptors, which may be advantageous in patients with vasoconstriction and hypertension, although it also causes dizziness more frequently than do other beta-blockers. Intrinsic sympathomimetic activity from partial beta-receptor agonism (as with xamoterol) has been detrimental. The beta-blockers most commonly prescribed for heart failure in the United States are carvedilol and extended-release metoprolol succinate. We await direct comparative data between these two drugs, but available information does not support the existence of a major clinical difference or a difference at the level of gene transcription in patients with a clinical response, as indicated in the article by Lowes et al. Currently, there is no need to substitute a new beta-blocker in patients who are already taking a beta-blocker at an effective dose.

### How to Titrate

Beta-blocker therapy is started at very low doses (carvedilol, 3.125 mg twice a day; extended-release metoprolol succinate, 12.5 mg daily). Initial doses are often doubled during the second week, with subsequent titration at intervals of two weeks or longer; several months may be required to achieve the maximal tolerated doses in patients with previous decompensation. Patients should be educated about signs of fluid retention and fatigue and should have frequent contact with their cardiac care team. Serial assessment of volume status and postural vital signs allows critical adjustment of the doses of diuretic agents and angiotensin-converting-enzyme inhibitors during beta-blocker therapy. A common reason for limiting dose escalation is bradycardia at a



A Funnel Diagram Showing Use of Beta-Blocker Therapy in Patients with a History of Myocardial Infarction, Asymptomatic Left Ventricular Dysfunction, or Stable Heart Failure.

For asymptomatic left ventricular dysfunction without coronary artery disease, beta-blockers are not currently recommended, but ongoing trials are deemed likely to show benefit. LVEF denotes left ventricular ejection fraction, and ACE angiotensin-converting enzyme.

heart rate below 60 beats per minute. Since there is concern that ventricular pacing may contribute to the progression of heart failure, implantation of a ventricular pacemaker solely to allow upward titration of beta-blockers cannot be advocated. Fatigue frequently occurs during upward titration, but many patients have no side effects; a small number, however, suffer from fatigue that persists for months and does not resolve until downward titration. Rarely, patients may have severe depression.

Although target doses of 25 to 50 mg of carvedilol twice a day and 100 to 200 mg of long-acting

metoprolol daily are advocated, the proportion of patients in whom these doses can be reached in trials exceeds that in the general population with heart failure, in which patients are at least 10 years older and coexisting conditions often prevail. Some patients will not tolerate beta-blockers at any dose, despite repeated attempts. Even low doses of beta-blockers confer benefit, however, and therapy should be continued if they are the only doses tolerated.

Further refinement of patient selection and dose selection must await deeper exploration of the mechanisms of beta-blocker thera-

py, as revealed in the article by Lowes et al. When we learn which functional and molecular changes are the causes and which changes are the results of recompensation, we can steer toward intermediate markers to guide adjustment of the overall regimen of beta-blockers with diuretics and angiotensin-converting-enzyme inhibitors to achieve maximal benefit from these therapies.

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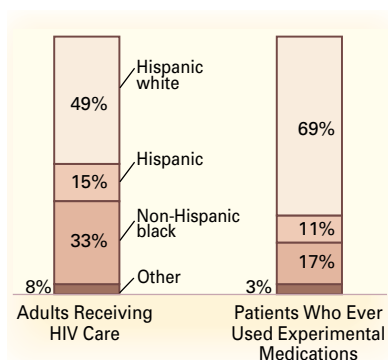


### Mycobacterial Boils after Footbaths at a Nail Salon

A physician in northern California reported four women who had multiple, culture-negative furunculoses of the lower extremities after pedicures at the same nail salon. Investigation identified an additional 106 customers with similar, persistent skin infections. All had had whirlpool footbaths before pedicures. The same strain of *Mycobacterium fortuitum* was isolated from 14 patients and three footbaths.

*For months this large outbreak was not recognized. At the nail salon, the source of contamination was traced to hair and skin debris that accumulated behind screens in the water inlets to the whirlpool footbaths. New regulations may be required to prevent infection in this setting.*

see page 1366



### Special Article: Access to Experimental Treatments for HIV Infection

There is concern that minority groups and women are underrepresented in research trials and are less likely to receive experimental treatments for human immunodeficiency virus (HIV) infection. This study of patients with HIV infection in the United States found that blacks and Hispanics were less likely to participate in trials than whites and to have received experimental medications. Women were not underrepresented in trials and were as likely as men to receive experimental treatments.

*According to this study, an estimated 14 percent of adults receiving HIV care have participated in a medication trial and about one quarter have received experimental medications. Although these rates are higher than those for patients with other diseases, there are substantial differences in access among racial and ethnic groups.*

see page 1373 (editorial, page 1400)



### Medical Progress: Bronchiectasis

Although bronchiectasis (permanent dilatation of the bronchi) is now uncommon, it has the potential to cause devastating illness. Chronic infection has an important role in its pathogenesis, and immunodeficiency states, cystic fibrosis, and primary ciliary dyskinesia may predispose patients to the condition. Diagnosis has been greatly facilitated by high-resolution computed tomography. This review article covers all aspects of the disorder, including recent approaches to therapy.

see page 1383



### Clinical Problem-Solving: One Foot Away

A 59-year-old woman with systemic lupus erythematosus, which was treated with 200 mg of hydroxychloroquine and 20 mg of prednisone per day, presents with fever, abdominal pain, and hematuria. She has received cyclophosphamide because of a history of lupus nephritis. Physical examination reveals a cushingoid appearance, a blood pressure of 90/50 mm Hg, suprapubic tenderness, and a mass on the dorsum of her left foot.

see page 1394