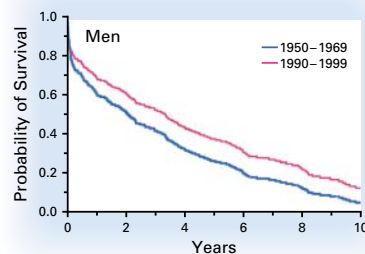




This Week in the Journal

October 31, 2002



Trends in the Incidence of and Survival with Heart Failure

Congestive heart failure has an extremely poor prognosis. This investigation from the Framingham Heart Study tracked trends over a 50-year period in the incidence of heart failure and in survival after its onset. During this period, the incidence of heart failure declined among women but not among men, whereas survival improved among both men and women.

Despite substantial improvement during the study period, overall survival rates among patients with heart failure remained below 50 percent at five years, pointing to the urgent need for better means of preventing this serious health problem.

see page 1397 (editorial, page 1442)



Increased Mortality among Women with Heart Failure Treated with Digoxin

The Digitalis Investigation Group previously reported no difference in mortality between patients with heart failure who received digoxin and those who received placebo. In this post hoc analysis, men and women in the trial were analyzed separately. Digoxin therapy had no effect on mortality in men but was associated with an increase in overall mortality among women (33.1 percent in the digoxin group vs. 28.9 percent in the placebo group).

Although derived from a post hoc analysis, the findings raise important questions about — and call for a reexamination of — the use of digoxin in the treatment of heart failure in women.

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PERSPECTIVE

Digoxin — New Perspective on an Old Drug

After all, in spite of opinion, prejudice or error, Time will fix the real value upon this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind.

— William Withering, 1785

Since 1785, when Sir William Withering published his treatise on the use of foxglove, our perspective on the use of digitalis has continued to change. Withering believed that digitalis had a diuretic effect in patients with a weak and irregular pulse who had edema.

Only in the early 20th century did digitalis begin to be considered useful in patients with heart failure and normal cardiac rhythm. The hemodynamic effects of digoxin were elucidated in the 1970s, when heart failure was understood to result from diminished function of the left ventricle, which could be ameliorated by decreasing the load on the heart with vasodilators or increasing contractility with inotropic drugs. During this period, three challenges to digoxin therapy were a high incidence of digoxin intoxication, newer promising therapies involving inotropic drugs that had vasodilator properties, and a perceived increase in mortality associated with the use of digoxin in patients who had had myocardial infarctions.

In the 1980s, there was renewed interest in digoxin for several reasons: there was a decrease in the incidence of digoxin intoxication because a lower dose was being used

and because it was understood that drug interactions (e.g., with quinidine) could increase serum digoxin levels; newer inotropic drugs were shown to be associated with poorer survival rates; and several trials demonstrated the potential benefit of digoxin in patients with heart failure and normal cardiac rhythm.

In the late 1980s, there was a paradigm shift emphasizing the importance of neurohormonal abnormalities in the progression of heart failure. During this time, it was discovered that digoxin, in addition to improving hemodynamics, had important neurohormonal modulating effects (for example, it reduces plasma renin and norepinephrine levels). In spite of these findings, the importance of digoxin was again questioned with the advent of more specific neurohormonal modulators (angiotensin-converting-enzyme [ACE] inhibitors and beta-blockers). More important, studies of the effect of digoxin on mortality were lacking.

In the mid 1990s, the results of the Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) trial and the Digitalis Investigation Group (DIG) trial prompted the Food and Drug Administration to approve digoxin under current regulations for the treatment of heart failure. The RADIANCE trial examined the effects of discontinuation of digoxin in stable patients with heart failure who were receiving diuretics and ACE inhibitors. The discontinuation of digoxin was associated with an increase by a factor of five in the rate of worsening heart failure within three months and a decrease in exercise tolerance within that period, in spite of the continuation of therapy with diuretics and ACE inhibitors.

The DIG trial was the first large



Courtesy of the Mary Evans Picture Library.

trial whose main objective was to assess the effect of digoxin therapy on overall mortality in patients with heart failure. The study enrolled 6801 patients who had systolic dysfunction while receiving diuretics and ACE inhibitors, half of whom had not received digoxin therapy. They were randomly assigned to receive a mean daily dose of 0.25 mg of digoxin or placebo. At 37 months after randomization, overall mortality was 35 percent, with no difference between the placebo group and the digoxin group. There was a 12 percent reduction in the rate of death due to pump failure with digoxin that was offset by an increase in the rate of death presumed to result from arrhythmia. Digoxin was associated with a significant reduction in the rate of death or hospitalization for worsening heart failure. Prespecified sub-



Skin Ulcers Misdiagnosed as Pyoderma Gangrenosum

It can be difficult to distinguish pyoderma gangrenosum from other causes of cutaneous ulceration. In this study, the authors identified 95 patients with skin ulcers that resembled pyoderma gangrenosum. The ulcers were actually caused by vascular occlusive or venous disease, vasculitis, cancer, infection, drug-induced or exogenous tissue injury, or other inflammatory disorders. Most patients who received a diagnosis of pyoderma gangrenosum were treated, and 36 percent of those who were treated had exacerbation of their underlying condition or a delay in its diagnosis.

Pyoderma gangrenosum is a diagnosis of exclusion. In patients in whom pyoderma gangrenosum is suspected, evaluation for alternative causes of cutaneous ulceration is important.

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group analyses suggested that the patients who had the greatest benefit were those who had cardiomegaly on chest radiography, a very low ejection fraction (<0.25), or severe symptoms.

Digoxin has a narrow therapeutic window. In patients with normal cardiac rhythm, the beneficial hemodynamic, neurohormonal, and clinical effects are found with a low dose that results in a serum concentration of approximately 0.7 ng per milliliter. Additional clinical benefits are not seen at higher doses traditionally considered to be therapeutic (with serum concentrations of 1.0 to 1.5 ng per milliliter). These higher doses may only predispose patients to arrhythmias. The DIG trial led to the hypothesis that digoxin may have a bidirectional effect on mortality related to the serum concentration — a beneficial effect at serum concentrations lower than 1.0 ng per milliliter and a detrimental effect at concentrations of 1.0 ng per milliliter or higher. Since digoxin therapy may result

in adrenergic stimulation at higher concentrations or in patients with ischemia, the combination of digoxin and beta-blockade may have theoretical advantages. Beta-blockers produce an anti-ischemic, anti-adrenergic effect leading to biologic improvement in function, while digoxin maintains hemodynamic compensation.

In this issue of the *Journal*, Rathore et al. (pages 1403–1411) report the results of a retrospective analysis of data from the DIG trial; they found a 4.2 percent increase in mortality with digoxin therapy in women but no such effect in men. As they acknowledge, a post hoc analysis may result in spurious findings as a result of chance alone or an imbalance in base-line characteristics between the treatment groups. The latter may have been the case, since the serum concentrations at one month were significantly higher in women than in men, and the increase in mortality among women may have been due to the use of a digoxin

dose that was too high. Unfortunately, the investigators did not adjust for serum digoxin levels. What the investigators may have demonstrated is that digoxin use in women should be undertaken with greater attention to the appropriate dose. Perhaps the reduction in the rate of hospitalization for heart failure among women could have been achieved without an increase in mortality if a lower dose had been used. We should not abandon a therapy that may help women with heart failure. Rather, we should use a dose that will result in a serum concentration lower than 1.0 ng per milliliter.

ERIC J. EICHORN, M.D.

Medical City Dallas Hospital
Dallas, TX 75230

MIHAI GHEORGHIADÉ, M.D.

Northwestern University Medical School
Chicago, IL 60611

**Tuberculosis-Control Program,
India, 1993-2001**

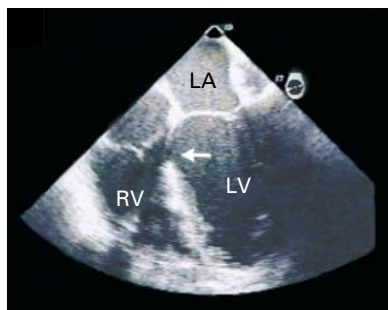
Treatment cards printed	>7 million
Microscopes purchased	>4,000
Medications purchased	>500 million
Laboratory technicians trained	6,187
Medical officers trained	22,735
Health workers trained	98,054

Special Article: Tuberculosis Control in India

In India nearly 500,000 people die each year from tuberculosis. Recent improvements in the national tuberculosis-control program are standardizing treatment, follow-up, and mandated reporting. More than 200,000 new health workers have been trained, and about 3.4 million patients have been evaluated. Nearly 800,000 patients have been treated, with a success rate of approximately 83 percent. The cost is about \$50 per patient treated.

The tuberculosis-control program in India is one of the largest public health efforts in the world. The national program has become more effective, but it still reaches less than half the population. Continued expansion is important, since India accounts for roughly one third of all the cases of tuberculosis in the world.

see page 1420 (editorial, page 1444)



Current Concepts: Rupture of the Interventricular Septum

When ventricular septal rupture complicates acute myocardial infarction, the mortality rate is high and immediate operative intervention is indicated. This review explains that septal rupture has become less common with reperfusion therapy but that rapid diagnosis remains crucial. Doppler echocardiography is usually diagnostic and can be used to estimate the size of the left-to-right shunt.

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“Tens of thousands of children are participating in studies of medications. The new research has been stimulated by a carrot and a stick.”

Health Policy Report: Testing Medications in Children

To stimulate more evaluation of the safety and efficacy of medications in children, two federal regulations were established. The pediatric exclusivity provision gives an additional six months of patent protection to companies that voluntarily test a medication in children, whereas the pediatric rule requires pediatric studies if a drug is important for children.

More children are being enrolled in clinical trials. The long-term effect will depend on the ethical and effective conduct of the research and the government’s continued commitment to assessing the safety and efficacy of drugs in children.

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