Use of digoxin in heart failure

Should we bother?

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Research question
What is the actual effect of digoxin on mortality from any cause and on hospitalization for heart failure?

Type of article and design
Randomized, double-blind, placebo-controlled trial of therapy.

Relevance to family physicians
The editorial accompanying this article called the debate about use of digoxin "...the oldest controversy in medicine." Most of the debate regarding digoxin has revolved around its possible efficacy and control of symptoms versus its possible toxicity. Trials supporting use of digoxin have been questioned because participants usually were "withdrawn and then put back on digoxin and there were questions about the impact of this withdrawal effect." As well, the trials were short and did not delineate digoxin's actual effect on cardiovascular events.

From the other side, we often wonder whether the risk of digoxin toxicity is worth it. Many of our patients with congestive heart failure (CHF) receive digoxin and have used it for many years. Recent guidelines have endorsed angiotensin-converting enzyme (ACE) inhibitors in combination with nonpharmacologic measures as the mainstay of treatment, with use of diuretics as needed, especially for patients with an ejection fraction (EF) under 35% to 40% or over 45% with primarily diastolic dysfunction and for patients who have had heart attacks.

We need to be aware of minimizing precipitating factors (eg, ischemia, rhythm problems) and the fact that, since most guidelines have been published, some recent evidence has shown that carvedilol (a β-blocker) has reduced mortality over a 6-month period for patients with mild to moderate CHF. Where does digoxin fit? Should we withdraw digoxin from patients who are doing well with it? What is the risk of digoxin toxicity?

Overview of study and outcomes
With more than 7000 patients, this is the largest randomized trial of digoxin. The primary end point was mortality from any cause; the secondary end point was hospitalization for CHF. Patients were followed up for 3 to 5 years after enrolling at one of 302 clinical centres in the United States and Canada. The main trial (EF < 0.45) assigned about 6800 patients to either placebo or digoxin, and the ancillary trial (EF > 0.45) enrolled about 1000 patients into one of these two groups. Baseline characteristics were similar, including average age of 63.5 years; EF of 28.5; mostly men; mostly white; mostly (>80%) with four signs of CHF; and mostly receiving ACE inhibitors (94%), diuretics (82%), and possibly nitrates (43%). Average dosage was 0.25 mg of digoxin. Patients were followed up 4 and 16 weeks into treatment and then every 4 months after that. It should be emphasized that patients enrolled in this study had a normal sinus rhythm at the beginning of the trial.

Results
The main trial (EF < 0.45) indicated no significant differences in mortality (~35%) or deaths (~30%) specifically from cardiovascular causes. There was a trend toward lower risk of mortality from worsening CHF in the digoxin group (394 vs 449 deaths, 95% confidence interval [CI] 0.77 to 1.01; P = 0.06), but this was not quite statistically significant.
significant. Reflecting this, fewer patients in the digoxin group were hospitalized for worsening CHF (910 vs 1180, CI 0.66 to 0.79, P < 0.001). Total number in the digoxin group hospitalized was also significantly lower (1927 vs 2553). When death and hospitalization secondary to CHF were combined, the digoxin group did better.

Improvement in these two specific examples was seen immediately and was sustained. As might be expected, improvements were most marked in those with an EF below 0.25, those with enlarged hearts, and those in New York Heart Association functional classes III and IV. Digoxin toxicity was suspected more often in the digoxin group (11.9% vs 7.9%), and patients in the group were hospitalized more often for this reason (2.0% vs 0.9%). The ancillary trial mirrored the findings of the main trial.

Analysis of methodology

This is obviously a sophisticated trial with very similar treatment and control groups and appropriate blinding. There was excellent follow up and appropriate adherence to the study regimen. Serum digoxin levels were variable (0.5 to 2.0mg/mL), which might make us question the biologic plausibility of which level gave the best risk-benefit ratio for the patient. This variation, however, probably reflects standard clinical practice.

This trial used combined end points: death or hospitalization secondary to CHF. This raises two obvious concerns. The first is the difficulty of being sure that patients actually died of CHF because these patients are generally quite sick and vulnerable to many other lethal events (often in combination with heart failure). The second is the concept of combining end points. It can often be useful (eg, in all-cause mortality), but it also can make study results nonspecific. We have to beware that end points have not been combined just to get significance.

An example will illustrate this. When we are considering the validity of end points, we take the patient’s perspective. Do our patients feel the same about hospitalization as they do about death? (Many would prefer death to hospitalization!) It makes us wonder whether the combination of these two end points, although obviously connected, gives us meaningful clinical information.

Application to clinical practice

This trial essentially comes to two conclusions about use of digoxin in patients with CHF: digoxin does not increase survival; it does reduce hospitalizations. Use of digoxin reduced hospitalizations, however, by only 8%. In real terms this means that average family physicians would avoid only nine hospitalizations by treating 1000 patients with digoxin for 1 year. It would have been interesting if the authors had measured quality of life to see whether fewer hospitalizations translated into better quality of life and more freedom from symptoms for patients.

Bottom line

Should we rush out and take all our CHF patients off digoxin? No. It might help keep a small number of them out of hospital, and the risk of digoxin toxicity is very low. Should all our patients with CHF receive digoxin? No. Given the better evidence for use of ACE inhibitors and probably β-blockers to improve the chances of survival for our patients with CHF, digoxin probably will be relegated to occasional use for managing symptoms.

References