CRITICAL REVIEW FORM FOR THERAPY STUDY

Citation: The Digitalis Study Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *NEJM 1997;336:525-33*

Users' Guide:	
Are the Results Valid?	
Did experimental and control groups begin the study with a similar prognosis?	
Were patients randomized?	Yes. The randomization was stratified by LV function as well as by study site (302 sites).
Was randomization concealed?	Yes. The randomization was done through a coordination center and relayed to sites via telephone (i.e. the enrolling folks did not have any information about the randomization scheme.)
Were patients analyzed in the groups to which they were randomized?	Yes. Analysis was intention to treat.
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Table 1 on page 526 shows that the groups were equal at the start of the trial with respect to important prognostic factors.
Did experimental and control groups retain a similar prognosis after the study started?	
Were 5 important groups (patients, caregivers, collectors of outcome data, adjudicators of outcome, data analysts) aware of group allocation?	1. **patients:** yes, to some extent. The study began with placebo controls and patients blinded to study arm. However, in some patients (if clinical need arose) a switch was made to open label treatment. Measures were taken to minimize unblinding for patients and caregivers. However, there was acknowledgement that this was not always possible. 2. **caregivers**: yes with same caveat as above. 3. **collectors of outcome data:** yes- blinding was protected, even if clinicians were unblinded 4. **adjudicators:** yes- blinding was protected, even if clinicians were unblinded 5. **data analysts:** yes- blinding was protected, even if clinicians were unblinded
Aside from the experimental intervention, were groups treated equally?	Yes. There are no differences that we know of in important co-interventions. Specifically, large proportions of patients in both groups received an ACE-Inhibitors and diuretics in addition to Dig (94% vs. 81%)
Was follow-up complete?	Yes. The final status of 98.6% of patients is known at the end of the trial. In addition, the investigators comment on a sensitivity analysis (how sensitive the results would be to the 'worst' case scenario if all of the lost patients had the worst possible outcome). In this case, a sensitivity analysis showed that the 'lost' patients would not affect the overall mortality results, even if all had died.

What are the Results?

How large was the treatment effect?

Mortality was the primary outcome measure, however the hospitalization outcomes were also important. Reults are summarized in the table below:

Outcome	Digoxin	Placebo	RRR	ARR	NNT
Mortality	34.8%	35.1%	Nonsignificicant (p=0.8)		
Total hospital	64.3%	67.1%	4.1%	2.8%	36
CHF hospital	27%	35%	23%	8%	13
CV hospital	49.9%	54.4%	8.3%	4.5%	22

Note: Of course, suspected digoxin toxicity was a more frequent cause of hospitalization in the treated group.

How precise was the treatment effect?

95% Confidence Intervals are reported in the tables surrounding the risk ratios. Because the sample size is large for this trial, the CI's are fairly tight in general.

Table 2 (page 528) shows CI's for the Risk Ratios. The major outcomes (all cause, cardiovascular and heart failure) all include 1 (i.e. no difference)

For hospitalization outcomes in Table 3, however, (page 529) several important outcomes have CI's that do not include 1 and favor the treated group.

How can I apply the results to my patient care?

Were the study patients similar to my patient?

In some ways, yes: 86% of the patients in the trial were white, 84% were either NYHA class II or III, and 70% of patient had ischemic cardiomyopathy. However, only 27% were older than 70 years. All in all, however, it is likely that our patient is close enough in characteristics to the study population that the results may be applied to him.

In addition, there are some ways in which the study results are particularly helpful to our patient. Notably, in our patient the outcome of preventing hospitalizations may be of great interest to him. She explicitly reports that staying out of the hospital is an important goal for her (and her pets!)

Were all patient- important outcomes considered?

Yes. Most (if not all) clinically relevant outcomes were considered.

Are the likely benefits worth the potential harms and costs?

This may be a matter of weighing patient's values. For a patient who elects to be treated with digoxin, there will be the need to monitor therapy, draw frequent drug levels, and hold the risk of toxicity. However, for some, these issues will be offset by the possible benefit of avoidance of hospitalization. From a resource utilization point of view, the cost of the drug (cheap) and monitoring (not quite so cheap) will still be less than a single hospitalization.

It is fairly convincing from this large, well-designed trial that there is not a large difference in mortality overall when using digoxin. Thus the quality of life issues (including hospitalization) should predominate the discussion.