Digoxin increased risk of death in women, but not men, with heart failure


QUESTION: Does the effect of digoxin therapy differ in men and women with heart failure (HF) and depressed left ventricular systolic function?

Design
Randomised (allocation concealed)‡, blinded (participants, healthcare providers,† and data collectors), placebo controlled trial with up to 48 months of follow up.

Setting
302 clinical centres in the US and Canada.

Patients
5281 men (median age 64 y, 87% white, 30% New York Heart Association [NYHA] class II–III) and 1519 women (median age 66 y, 81% white, 40.6% NYHA class II–III) who had clinically confirmed HF (ie, current or past clinical symptoms or signs or radiographic evidence of pulmonary congestion) and an ejection fraction ≤ 45%. [Follow up was 99%]*

Intervention
2642 men and 755 women were allocated to digoxin, and 2639 men and 764 women were allocated to placebo. The initial recommended dose was based on a nomogram that accounted for age, sex, weight, and renal function (0.125–0.500 mg/d).

Main outcome measures
All cause mortality. Secondary outcome measures included death from all cardiovascular causes, death from worsening HF, hospital admission for worsening HF, and hospital admission for causes other than HF.

Main results
Analysis was by intention to treat. Results were adjusted for baseline variables. Men in the digoxin group did not differ from men in the placebo group for all cause mortality or cardiovascular death; women in the digoxin group had an increased risk of all cause mortality and cardiovascular death (table). Digoxin reduced death and hospital admission caused by worsening HF in men but not women (table). More men in the digoxin group than the placebo group had hospital admissions for other causes; in women, the groups did not differ (table).

Conclusion
Digoxin led to an increased risk of all cause and cardiovascular death in women, but not in men, with heart failure and depressed left ventricular systolic function.

†Information provided by author.

COMMENTARY
A systematic review of the effectiveness of digitalis glycosides in the treatment of HF in patients with normal sinus rhythm concluded that mortality did not differ between treatment and control groups, while patients treated with digitalis had a lower rate of hospital admission and clinical deterioration.1 What was missing from the studies reviewed was any exploration of possible sex differences in response to treatment.

Rathore et al addressed that gap through secondary analysis of a large data set collected by the Digitalis Investigation Group as part of a multicentre trial. Their finding that women receiving digoxin were significantly more likely to die than women who received placebo can be considered robust because the 2 groups did not differ significantly at baseline with respect to important predictors of mortality such as age or cause or severity of disease. Men, on the other hand, were not more likely to die when treated with digoxin compared with placebo. When compared with men, the women in the study were older and had greater severity of HF and greater comorbidity. Although the researchers adjusted for these differences in their analysis, the data were derived from a trial where exploration of sex differences was not planned a priori. This resulted in a disproportionate number of men in the secondary analysis, which could be considered a possible limitation.

Women already account for most deaths from HF, and these study findings indicate that the risk is increased for women taking digoxin. Unfortunately, the study was unable to test explanations for the difference. However, it is worthwhile for nurses working with women with CHF to question the need for digoxin in the treatment plan. This study also supports the need for studies that incorporate stratification for sex in their design and execution.

Elizabeth Rideout, RN, PhD
Associate Professor
McMaster University
Hamilton, Ontario, Canada


Digoxin v placebo for heart failure (HF) in men and women!

<table>
<thead>
<tr>
<th>Outcomes at ≤48 months</th>
<th>Sex</th>
<th>Digitalis</th>
<th>Placebo</th>
<th>Adjusted RRR (95% CI)</th>
<th>Adjusted NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>Men</td>
<td>35.2%</td>
<td>36.9%</td>
<td>6% (-2 to 12)</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>33.1%</td>
<td>28.9%</td>
<td>19% (2 to 36)</td>
<td>19 (10 to 207)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>Men</td>
<td>30.5%</td>
<td>31.1%</td>
<td>3% (-5 to 11)</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>27.8%</td>
<td>24.1%</td>
<td>20% (2 to 42)</td>
<td>21 (10 to 240)</td>
</tr>
<tr>
<td>Death from worsening HF</td>
<td>Men</td>
<td>11.4%</td>
<td>13.6%</td>
<td>20% (7 to 30)</td>
<td>38 (25 to 99)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>12.4%</td>
<td>11.9%</td>
<td>16% (-12 to 51)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Hospital admission for worsening HF</td>
<td>Men</td>
<td>25.8%</td>
<td>34.7%</td>
<td>29% (23 to 35)</td>
<td>10 (9 to 13)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>35.9%</td>
<td>32.2%</td>
<td>12% (-2 to 28)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Hospital admission for other causes</td>
<td>Men</td>
<td>39.9%</td>
<td>35.0%</td>
<td>13% (6 to 21)</td>
<td>22 (14 to 52)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>33.1%</td>
<td>28.9%</td>
<td>19% (2 to 36)</td>
<td>19 (10 to 207)</td>
</tr>
</tbody>
</table>

Data are derived from a trial where exploration of sex differences was not planned a priori. This resulted in a disproportionate number of men in the secondary analysis, which could be considered a possible limitation.

For correspondence: no information available.

Source of funding: National Heart, Lung, and Blood Institute.

Abbreviations defined in glossary. RRR, RRI, NNT, NNH, and CI calculated from control event rates and adjusted hazard ratios in article.
Digoxin increased risk of death in women, but not men, with heart failure

_Evid Based Nurs_ 2003 6: 80
doi: 10.1136/ebn.6.3.80

Updated information and services can be found at:
http://ebn.bmj.com/content/6/3/80

_These include:_

**References**
This article cites 3 articles, 0 of which you can access for free at:
http://ebn.bmj.com/content/6/3/80#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Drugs: cardiovascular system (278)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/