Digoxin therapy for heart failure: safe for women?

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William Withering's publication in 1785 of the monograph "An Account of the Foxglove, and Some of Its Medical Uses, with Practical Remarks on Dropsy and Other Diseases" first introduced digitalis, the extract of digitalis purpurea (the foxglove plant), to the medical armamentarium. Despite more than 200 years of experience with digitalis, its value in the management of patients with heart failure continues to be debated. Studies in the late 1970s first suggested that digitalis provides a positive hemodynamic effect to patients with heart failure in sinus rhythm[1,2]. Concerns of digoxin-associated toxicity and reports of increased mortality in patients treated with digoxin post-myocardial infarction, however, raised questions about the safety of digoxin use. Small randomized controlled trials conducted through the 1980s and early 1990s provided some additional information[3-5], but the effect of digoxin on major cardiovascular endpoints, including mortality and hospitalizations, remained unclear. This uncertainty was reflected in the large difference in rates of digoxin use both between and within countries[6].

The Digitalis Investigation Group (DIG) trial was designed to definitely establish the effect of digoxin on mortality. Conducted at 302 centers in the United States and Canada, the DIG trial evaluated digoxin in 6800 patients with stable heart failure and left ventricular systolic dysfunction in sinus rhythm in the main trial and 988 patients with heart failure and preserved systolic function in a parallel ancillary trial[7]. After a mean follow-up of 37 months, digoxin was found to have no effect on the trial's main endpoint of all-cause mortality and provided only a modest reduction for the secondary endpoint of hospitalizations[7]. Debate over the utility of digoxin has continued[8], but clinical practice guidelines issued since the DIG trial's publication endorse the use of digoxin in symptomatic heart failure patients[9-11]. Although the DIG trial investigators assessed the effect of digoxin therapy across multiple clinical subgroups, a sex-based subgroup analysis was not pre-specified or conducted[12].

There are good reasons to conduct a sex-based subgroup analysis of the DIG trial. Men and women are known to differ in the epidemiology, etiology, and prognosis of heart failure[13]. There has been a growing push for the inclusion of women in randomized controlled trials evaluating heart failure therapies[14] and current US Food and Drug Administration (FDA) regulations require that all new drug applications explicitly consider possible sex differences in drug effects[15]. Glaxo-Wellcome was not required to report sex-specific data for its new drug application for Lanoxin because the DIG trial preceded the FDA's regulation. Curiously, the Lanoxin package insert discussed digoxin's effect on racial subgroups, but makes no mention of assessing possible sex difference in digoxin efficacy (Lanoxin tablets, USP. Research Triangle Park, NC: GlaxoSmithKline, 2001). Similarly, the DIG trial investigators published a *post-hoc* age-based subgroup analysis, but did not report any data on possible sex differences in digoxin efficacy[16]. Given the recognized need to incorporate sex-stratified analyses into drug evaluations[17], we undertook a sex-based subgroup analysis of the DIG trial.

Our study, published in the October 31, 2002 issue of the *New England Journal of Medicine,* identified a statically and clinically significant interaction between patient sex and digoxin therapy[18]. Although digoxin has no effect on all-cause mortality among men, crude mortality rates were 4.2% higher in women randomized to digoxin compared with women randomized to placebo. The digoxin-associated increased harm persisted after robust multivariable adjustment, with women randomized to digoxin at a 23% increased relative hazard compared with women randomized to placebo. A similar pattern of increased harm or diminished benefit was observed when we compared women randomized to digoxin with women randomized to placebo for the endpoints of death from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, and hospitalization for other causes. Moreover, this pattern of increased harm among women randomized to digoxin persisted over the full length of the DIG trial. This increased mortality risk translates into an additional 161 deaths among 10 000 women taking digoxin each year. In contrast, the Women's Health Initiative study was recently stopped because of 19 excess events (not deaths) for every 10 000 women randomized to estrogen/progestin for 1 year[19]. Although *post-hoc* subgroup analyses must be evaluated cautiously[20], the size of the mortality risk we identified suggests a re-examination of the role of digoxin in the treatment of women with heart failure merits consideration.

The perspective accompanying our article suggested that the digoxin-associated harm in women was attributable to higher serum digoxin concentrations observed in women[21]. This comment is based on a review paper by Gheorghiade and Pitt[22] that suggested that there was an association between serum digoxin concentrations and mortality in the DIG trial, even among patients within the DIG trial's therapeutic range (0.5 to 2.0 ng/ml). However, as others have noted, the primary data supporting this conclusion have not been published in any peer-reviewed journal[23] and thus the relative accuracy of 1.0 ng/ml serum digoxin threshold suggested by Eichhorn and Gheorghiade[21] merits closer examination.

Although serum digoxin concentrations may contribute to some of the increased digoxin-associated risk observed in women, we do not believe that sex differences in serum digoxin concentrations fully explain the digoxin-associated harm observed in women in the DIG trial. We base our opinion on the following points. First, the DIG trial employed a dosing nomogram that included sex and renal function in order to ensure that patients received digoxin doses that would achieve serum concentrations within the therapeutic range. The general similarity in serum digoxin concentrations across the four dosing groups speaks to the general success of this algorithm[23]. Second, sex differences in serum digoxin concentrations were small (0.9 ng/ml women vs 0.8 ng/ml men) and only observed at 1 month post-randomization. There were no sex differences in serum digoxin concentrations at 12 months post-randomization[18], suggesting a sex difference in serum digoxin concentrations that was transient and limited to the initial period of the DIG trial. Given that the digoxin-associated mortality risk in women was observed over the full length of the DIG trial, this would also suggest a process other than confounding by sex differences in serum digoxin concentrations. We did not report the results of the sex and digoxin interaction evaluation using serum digoxin concentration because serum digoxin levels were only drawn for 2168 randomly selected patients in the DIG trial, a cohort that is too small to provide a definitive analysis of a sex and digoxin therapy interaction of the size reported in our analysis. However, in this underpowered cohort, the parameter estimate for the sex and digoxin therapy interaction term was 1.15 (95% confidence interval 0.87-1.54) for all-cause mortality. A point estimate above 1.00 indicates that digoxin was associated with an increased risk of mortality in women, even after accounting for sex differences in serum digoxin concentrations. This analysis would suggest that sex differences in serum digoxin concentration may, at most, confound the sex and digoxin therapy interaction we observed, but do not entirely account for the increased mortality in women randomized to digoxin. Any digoxin-associated increased risk in women has likely not been suspected previously because of the markedly poor survival of patients with heart failure in the community. In a population in which fewer than 40% of patients survive more than 5 years after initial diagnosis, an excess mortality risk of 4% would likely be unnoticed[24].

How then should our findings be integrated with the main results of the DIG trial? The DIG trial reported that digoxin had no effect on mortality and provided only a modest 6% reduction in all-cause hospitalizations. As yet unpublished analyses by the DIG trial investigators suggest that digoxin did not demonstrate improvements in quality of life or exercise tolerance greater than that seen by patients randomized to placebo[25]. Thus, the sole demonstrated benefit of digoxin therapy is a small reduction in the DIG trial's secondary endpoint of all-cause hospitalization. This modest proven benefit must then be balanced against our finding of a suggested digoxin-associated harm in women. Because of the known limitations of subgroup analyses, our findings necessarily reside on a weaker evidentiary base than the results of the main DIG trial. However, there is no clear method for balancing different sources of evidence when the competing claims involve weighing a "known small benefit" with those of "possible substantial harm". Although some women may consider the benefits of digoxin therapy sufficient to merit a possible increased risk of mortality, we doubt that most patients would agree, particularly given other agents available to manage heart failure today. Indeed, the possible risk of digoxin-associated in mortality is suffi-

ciently high and the clinical benefits so modest that we do not believe digoxin would pass regulatory approval were it submitted for evaluation as a new drug today.

Physicians may be wondering how to incorporate the results of our findings into their daily practice. We have suggested to our colleagues that digoxin plays a diminished role in the management of adults with heart failure who are in sinus rhythm. Patients should first achieve maximal therapy with angiotensin-converting enzyme inhibitors and beta-blockers. These therapies can reduce mortality and still remain underutilized[26,27]. The decision to use digoxin therapy in women who remain symptomatic on maximal therapy should be based, in large part, on their treatment objectives. Women seeking to reduce their risk of hospitalization, and not survival, may be willing to accept the possible mortality risk associated with digoxin therapy. However, for women concerned with decreasing their risk of mortality, we would suggest they not consider digoxin therapy. Although some commentators believe that digoxin would be beneficial for women at lower doses, this is a testable hypothesis that currently available evidence cannot address. Women on digoxin therapy should tailor their decision to continue or withdraw digoxin based on these same treatment objectives. Further, recent data suggest that digoxin withdrawal may be safer in the beta-blocker era. Crucial to any treatment decision is a conversation between women and their physicians about the balancing of a possible mortality risk with a relatively modest clinical benefit.

In conclusion, our analysis of the DIG trial identified a digoxin-associated risk of increased mortality in women that persisted after multivariable adjustment. Although based on a subgroup analysis, we believe the possibility of increased mortality among women taking digoxin is sufficient to outweigh digoxin small reduction in hospitalizations for patients with heart failure in sinus rhythm. Our findings underscore the need to consider sex or sex-associated interactions when evaluating therapies, both in the design and conduct of randomized controlled trials and in observational evaluations of therapies in daily clinical practice. With women comprising more than half of all patients who develop heart failure[28], the impetus for sex-oriented analyses of heart failure therapies is clear.

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