

Reducing HF Hospitalizations with Digoxin: A Closer Look at the DIG Trial

A Discussion Between Dr. Ali Ahmed and Dr. Michel White

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Q: Dr. Michel White: What was the primary motivation behind conducting such a comprehensive post-hoc analysis of the Digitalis Investigation Group (DIG) trial?

A: Dr. Ali Ahmed: Digoxin is the oldest heart failure (HF) drug and probably the least expensive one. There is a wealth of data, including the 1997 DIG Trial,¹ showing that its use is associated with reduction in HF hospitalization without an increase in mortality.

Despite this evidence, data suggests that the use of digoxin is declining in North America. In addition, as clinicians in developing nations might follow practice patterns in developed nations, there is a real possibility that millions of HF patients in the developing world, who cannot afford angiotensin-converting enzyme (ACE) inhibitors or beta-blockers, would be deprived of digoxin.

In this context, we recently decided to go beyond subgroup analyses and conduct the most comprehensive post-hoc re-analysis of the DIG trial.²

Q: Please summarize the characteristics of the original DIG cohort, including background medications.

A: There were 6,800 HF patients with ejection fraction (EF) \leq 45% and 988 patients with EF $>$ 45%, all of whom were in normal sinus rhythm. They were recruited from the United States (186 centers) and Canada (116 centers) between January 1991 and August 1993.

Patients were approximately 80% male and 85% Caucasian with a mean age of about 64 years. Approximately two thirds of patients had mild to moderate chronic HF (NYHA class I-II symptoms), over 60% had history of previous myocardial infarction and over 40% had known history of hypertension. Over 80% were receiving diuretics and over 90% were on ACE inhibitors. Data on

concomitant use of beta-blockers was not collected. However, because beta-blockers were not approved for use in HF at the time of the trial, it is reasonable to assume that not many DIG participants were receiving these agents.

Q: What segment of the original DIG cohort did you examine in this new post-hoc analysis? How did you assign patients to groups?

A: Because we wanted to account for serum digoxin concentration (SDC), we restricted our analysis to the DIG participants who had SDC based on specimens collected at least six hours after the last dose. SDC was measured in a random subset of DIG patients one month after randomization, and investigators were blinded to those results.

The total number of digoxin patients with SDC data in our analysis was 1,687 (of 3,889 random-

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ized to digoxin). We categorized these patients into those with low SDC (0.5 - 0.9 ng/mL, $n = 982$) and those with high SDC (≥ 1.0 ng/mL, $n = 705$). These cut points were chosen because of their significant association with outcomes in previous studies.^{3,4}

As a control group, we also included 3,861 of the 3,899 patients randomized to placebo who were alive at one month. The total cohort for our analy-

sis was therefore 5,445 (of the 7,788 DIG participants).

Q: Were there significant baseline differences in other parameters between the high- and low-SDC patients? Did these differences affect outcomes?

A: Compared to placebo patients, those with low SDC were younger, had lower NYHA class symptoms, had lower mean serum creatinine, were less likely to have pulmonary congestion and were less likely to receive diuretics. Those with high SDC were the opposite: compared to placebo patients, they were older, had higher mean serum creatinine, were more likely to have pulmonary congestion and higher NYHA class symptoms and were more likely to receive diuretics.

To address this and other potential imbalances in baseline covariates, we used propensity score matching. We were able to match all 982 low-SDC patients and all 705 high-SDC patients with placebo patients with similar propensity scores. The standardized difference was 8% or lower in absolute value for all covariates and interactions in the 982 low-SDC matched pairs and the 705 high-SDC matched pairs (a standardized difference of < 10% in absolute value indicates adequate balance).

Q: Please summarize your observations regarding all-cause, cardiovascular (CV) and HF mortality.

A: Among patients receiving placebo, 33% died of any cause, compared with 29% of those with low SDC

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and 42% of those with high SDC. Low SDC was associated with a 22% relative risk reduction compared to placebo. When adjusted for other covariates, low SDC remained associated with a significant 23% reduction.

High SDC was associated with a 23% relative increase in unadjusted mortality versus placebo. This was not unexpected, as these patients were considerably sicker than placebo patients at baseline. After adjusting for the baseline differences (e.g., age, NYHA class, etc.), however, we found that high SDC was no longer an independent predictor of mortality.

Similar associations were observed for both CV and HF mortality.

Q: What did you find in terms of impact on hospitalizations?

A: Overall, 67% of participants were hospitalized, of which 53% were due to CV causes and 31% due to worsening HF.

Compared with 33% of placebo patients, 23% of those with low SDC and 29% of those with high SDC were hospitalized due to worsening HF. After multivariable adjustment, low SDC was associated with a significant 38% reduction in HF hospitalization and an 18% reduction in all-cause hospitalization. High SDC was associated with a significant 22% reduction in HF hospitalization, but there was no reduction in all-cause hospitalization.

Q: Some post-hoc analyses of the DIG trial reported that certain subgroups of patients were at increased risk of mortality from digoxin. How do you interpret these results?

A: A post-hoc analysis of the DIG trial, published in 2002, showed that digoxin use was associated with increased mortality in women.⁵ However, two subsequent independent analyses of the DIG data, conducted independently and published almost simultaneously in two different journals^{4,6} did not replicate this finding. They did not find any digoxin-related increase in mortality in women. A separate analysis using the Studies of Left Ventricular Dysfunction (SOLVD) dataset also reported no significant interaction between digoxin and sex.⁷ This lack of interaction has now been even further validated by our analysis.²

Another post-hoc subgroup analysis indicated that high SDC was associated with increased mortality in a bivariate analysis of men with systolic HF.⁸ As is the case with our analysis,² however, when adjusted for other covariates, high SDC was not significantly associated with increased mortality in that study.

Q: What are your recommendations for digoxin dosing?

A: The beneficial hemodynamic and neurohormonal properties of digoxin seem to be optimum at low SDC. We found that only low SDC was associated with reductions in total mortality and total hospitalizations.

To reduce the odds of developing a high SDC, we rec-

ommend that digoxin be used in lower doses.² After multivariable adjustment, we found that the odds of developing high SDC increased dramatically at doses greater than 0.25 mg. Based on this data, we recommend a daily dose of 0.25 mg or lower for young men with clinically stable HF (no pulmonary congestion by chest x-ray and not receiving diuretics) and normal renal function.

Dosing should, however, be influenced by other patient characteristics, such as age, sex, kidney function and pulmonary congestion or diuretic use. When any of these risk factors for high SDC is present, a daily dose of 0.125 mg would probably be more appropriate. If two or more risk factors for high SDC are present, a daily dose of 0.0625 mg, or 0.125 mg every other day, should be considered.

Q: How do you initiate and monitor treatment? Do you perform SDC on a regular basis?

A: We recommend that in patients with multiple risk factors for high SDC, it may be preferable to measure SDC whenever possible to guide therapy. It may also be cost-effective to measure SDC in all patients receiving digoxin, if it allows us to achieve a low SDC. The costs of testing would likely be offset by reduction in non-HF hospitalizations. This would be even more effective should newer generations of inexpensive and more reliable SDC measurements become available.

Q: In the DIG trial, patients were not receiving beta-blockers or aldosterone antagonists. Do you believe digoxin would result in a similar impact on outcomes in the context of such therapies?

A: A post-hoc analysis of the U.S. Carvedilol Trials data⁹ demonstrated that digoxin use was associated with a significant reduction in the combined endpoint of death or hospitalization from all causes in patients with or without beta-blockers. In the RALES trial,¹⁰ the survival benefit of spironolactone was only significant in patients receiving digoxin.

There is, therefore, no reason to withhold digoxin from HF patients receiving beta-blockers or aldosterone antagonists, and in fact digoxin should be an important part of the HF treatment regimen.

Q: It has been reported that digoxin prescriptions are decreasing for HF patients. To what do you attribute this decline?

A: There are several possible reasons. First, mortality benefit is considered the gold standard in HF trials. Because

of a perceived lack of mortality benefit, digoxin was viewed negatively, with its important benefit of reducing HF hospitalization being largely forgotten. Second, expensive, device-based therapies are being aggressively promoted for relief of HF symptoms without mentioning the role of digoxin. Third, there have been concerns

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among some clinicians regarding whether the benefit of digoxin extend to today's HF patients in the beta-blocker era. Fourth, there has been a lack of industry promotion of digoxin and lack of a scientific discussion about the role of digoxin at annual meetings of major cardiology organizations. Fifth, some clinicians have been concerned about the safety of digoxin in women with systolic HF and in men with systolic HF and high SDC. Finally, there is a lack of data on the role of digoxin in diastolic HF patients, who comprise about half of all HF patients.

Q: Based on your findings, what do you believe should be the place of digoxin in HF therapy?

A: As pointed out by Professor Dr. Brophy in the editorial accompanying our paper,¹¹ there is a need to “rehabilitate” digoxin for HF care. The effect of digoxin in reducing hospitalization is very substantial. About 11 patients need to be treated with digoxin for three years to avoid one costly HF hospitalization. Digoxin was used as a background therapy in most clinical trials of HF. Drugs such as ACE inhibitors or beta-blockers may be beneficial regardless of digoxin. However, as Dr. Brophy pointed out, this is not known with certainty. It is also

References:

1. Digitalis Investigation Group: N Engl J Med 1997;336(8):525-33.
2. Ahmed A, et al: Eur Heart J 2006;27(2):178-86.
3. Adams KF Jr, et al: J Am Coll Cardiol 2002;39:946-53.
4. Adams KF Jr, et al: J Am Coll Cardiol 2005;46:497-504.
5. Rathore SS, et al: N Engl J Med 2002;347(18):1403-11.
6. Ahmed A, et al: Eur J Heart Fail. 2005 Nov 24; [Epub ahead of print].
7. Domanski M, et al: J Card Fail 2005;11(2):83-6.
8. Rathore SS, et al: JAMA 2003;289(7):871-8.
9. Eichhorn EJ, et al: Am J Cardiol 2000;86:1032-5.
10. Pitt B, et al: N Engl J Med 1999;341:709-17.
11. Brophy JM: Eur Heart J 2006;27(2):127-9.