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Digoxin and reduction in mortality in systolic and diastolic heart failure at low serum digoxin concentrations

The DIG trial is the largest trial of digoxin and a very important trial that is not likely to be replicated soon. Therefore, the analyses of Ahmed et al.1 is useful and welcomed. One important conclusion of their study is that ‘SCD 0.5–0.9 reduced mortality in a wide spectrum of HF patients and had no interaction with ejection fraction (EF) >45% (P = 0.834).’ However, their Figure 4 shows that in patients with EF >45% and SDC 0.5–0.9 ng/dL, the HR (95% CI) for all-cause mortality was not ‘significantly’ better than placebo. Is this correct? What were the numbers of patients in these subgroups? It would be most helpful if the authors provided Kaplan–Meier curves of mortality and of hospitalization in those with EF >45% and SDC 0.5–0.9 vs. placebo and probably also vs. higher SDC.

Of interest: (i) all-cause mortality in placebo and SDC 0.5–0.9 was similar to our analysis, if one excluded deaths due to ‘probable’ and ‘possible’ digoxin toxicity; (ii) it is particularly gratifying that they have dedicated their article to the memories of Thomas W. Smith, M.D. and Richard Gorlin, M.D. as was done in an earlier article.3

References
1. Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Crouse Jr JI, Pfeffer MA, Gheorghiade M, Gheorghiade M, Digitalis Investigation Group (DIG) trial. Our subgroup analysis based on low SDC and placebo patients included 4843 patients: 982 patients receiving digoxin who had low SDC and 3861 patients receiving placebo. Of these, 602 (12%) had diastolic HF: 108 patients with low SDC and 494 patients receiving placebo. The magnitude of the absolute and relative reductions in total mortality was comparable between patients with systolic and diastolic HF, and there was no significant heterogeneity in the effect of digoxin between these two groups (adjusted P for interaction 0.834).1


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Digoxin and reduction in mortality and hospitalization in systolic and diastolic heart failure at low serum digoxin concentrations: reply

We appreciate Dr Rahimtoola’s comments regarding our recent report1 based on the Digitalis Investigation Group (DIG) trial. Our analysis, which included both men and women with systolic (ejection fraction ≤45%; main trial) or diastolic (ejection fraction >45%; ancillary trial) heart failure (HF), confirmed one of the key findings of the DIG trial that digoxin significantly reduces hospitalizations due to worsening HF in a broad population of HF patients with sinus rhythm.2

Our study also demonstrated that digoxin reduces hospitalization regardless of serum digoxin concentrations (SDC). Furthermore, we observed that in patients who achieved low SDC (0.5–0.9 ng/mL), digoxin was associated with reduction in all-cause mortality and all-cause hospitalizations.1 In a subgroup analysis, we found no significant interaction between digoxin and any major patient characteristic, including sex and ejection fraction.

Our subgroup analysis based on low SDC and placebo patients included 4843 patients: 982 patients receiving digoxin who had low SDC and 3861 patients receiving placebo. Of these, 602 (12%) had diastolic HF: 108 patients with low SDC and 494 patients receiving placebo. The magnitude of the absolute and relative reductions in total mortality was comparable between patients with systolic and diastolic HF, and there was no significant heterogeneity in the effect of digoxin between these two groups (adjusted P for interaction 0.834).1

We thank Dr Rahimtoola for his comments. However, the bulk of the dietary intervention low in fat and high in fruit and vegetables might have been dampened by reducing the intake of nuts. A Western dietary pattern should be avoided in patients with acute coronary syndromes; however, the best recipe has to be defined.

References

recurring coronary events, and also improved endothelial function, inflammation, and insulin resistance in subjects with the metabolic syndrome. The importance of the whole-diet approach is best defined by the results of the Women Health Initiative showing that a dietary intervention low in fat and high in vegetables and fruits did not reduce the risk of cardiovascular events in postmenopausal women. However, the bulk of the dietary intervention was focused on substitution of fats with carbohydrates, in a quite similar exchange (–8.2% energy from fat vs. +8.1% energy from carbohydrates). Unfortunately, the reduced fat intake was stratified across all fat categories, including those with supposed or proven beneficial effects on cardiovascular health, such as monounsaturated and polyunsaturated fats. Following this line of reasoning, the healthy effect of increasing fruit and vegetables might have been dampened by reducing the intake of nuts.