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Low-Dose Digoxin and Reduction in Mortality and Morbidity in Heart Failure

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We thank Drs. van Veldhuisen and de Boer for their insightful comments regarding our recent report based on the Digitalis Investigation Group (DIG) trial [1]. We agree that digoxin should continue to play an important role in the management of heart failure [2,3]. However, unfortunately digoxin continues to be underutilized in clinical practice [4]. This may be due to a lack of scientific discussion at national meetings, a lack of industry promotion, and an overemphasis on mortality over hospitalization as outcomes [5]. This latter reason is particularly ironic as hospitalization due to worsening heart failure, common in heart failure, is reduced by digoxin regardless of serum concentrations or daily dosages [6]. The introduction of beta-blockers since the DIG trial may also have contributed to the underuse of digoxin [5].

Most heart failure patients are older adults and we agree that beta-blockers are safe and well tolerated in elderly systolic heart failure patients [7–10]. In the SENIORS trials, nebivolol significantly reduced the primary combined end point of all-cause mortality or cardiovascular hospitalization in elderly heart failure patients, but had no significant effect on individual components of that composite end point [7]. In the MERIT-HF trial, metoprolol extended release was as effective in the elderly as in the younger heart failure patients [9]. However, heart failure patients enrolled in major beta-blocker trials were over a decade younger than typical heart failure patients seen in clinical practice [4,10].

Mortality and morbidity in contemporary heart failure patients receiving beta-blockers and other neurohormonal antagonists remain high and many subsequent clinical trials using other interventions have failed to further improve outcomes. Yet, the role of digoxin in these patients is often questioned as the DIG trial was conducted before the beta-blocker era of heart failure therapy. Although this issue can only be definitively resolved with a large randomized clinical trial of digoxin in contemporary heart failure patients receiving beta-blockers, data from post-hoc analysis of beta-blocker trials suggest that digoxin and carvedilol may be equally effective in the presence or absence of each other. Digoxin reduced the combined endpoint of all-cause death or all-cause hospitalization in patients receiving carvedilol (relative risk {RR}, 0.64; 95% confidence interval {CI}, 0.52 to 0.79) and placebo (RR, 0.82; 95% CI, 0.71 to 0.99) [11]. Carvedilol, on the other hand, had similar effect on combined endpoint in patients receiving (RR, 0.63; 95% CI, 0.52 to 0.75) and not receiving (RR, 0.80; 95% CI, 0.64 to 1.00) digoxin [11]. A plausible explanation of

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this synergy may be that by reducing digoxin-induced serious arrhythmias, beta-blockers enhance the effectiveness of digoxin, and by providing inotropic support, digoxin improves the tolerability for beta-blockers.

All major beta-blocker trials in heart failure excluded patients with diastolic heart failure, who constitute nearly half of all elderly heart failure patients. Data from the DIG ancillary trial suggest that digoxin may play a role in the management of diastolic heart failure [12]. The effects of digoxin in these patients were very similar to those of candesartan, the only other drug tested in diastolic heart failure in a large randomized clinical trial [5,12]. Digoxin was better tolerated and patients receiving digoxin had fewer adverse effects than those receiving candesartan [5]. Digoxin is also inexpensive, an important consideration for millions of heart failure patients in the developing world, whose left ventricular ejection fraction often cannot be known.

The safety and effectiveness of digoxin in elderly heart failure patients has been documented in a post-hoc analysis of the DIG trial [13]. Findings from that analysis suggest that the use of digoxin in low doses (≤ 0.125 mg/day) was a strong predictor of low serum concentrations, which was significantly associated with reduced mortality and hospitalization in these patients [13]. However, in frail elderly heart failure patients with impaired kidney function, even a lower daily dose (0.125 mg every other day) may be preferable [13].

For a definite resolution of the role of digoxin in contemporary heart failure patients, a second multicenter randomized clinical trial of digoxin is warranted. This trial should be designed to include equal representations of men and women, whites and non-whites, and systolic and diastolic heart failure patients. However, there may not be enthusiasm in the industry to fund such a trial. We therefore hope that public international funding would be made available to support a definitive trial of digoxin in contemporary heart failure in the greater public health interest.

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