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Editor's Note

Digitalis Glycosides for Heart Rate Control in Atrial Fibrillation

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Digitalis glycosides were first introduced into clinical use in 1785 by William Withering, a physician in Birmingham, England.[1] A new study published in *JAMA*, also conducted by physicians in Birmingham, provides novel information on the use of digoxin for heart rate control in patients with atrial fibrillation (AF).[2]

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To slow the ventricular response rate in patients with AF, clinical practice guidelines in both the US[3] and in Europe[4] stipulate the use of β-blockers or calcium channel blockers as the drugs of first choice.

Previously, digitalis glycosides have also been used for this purpose. By a mechanism that is not fully understood, digitalis compounds increase vagal efferent activity to the heart, and this parasympathomimetic action reduces conduction velocity of electrical impulses through the atrioventricular node, thus slowing ventricular response rate in AF. In 2014, the TREAT-AF study[5] found that the use of digoxin for heart rate control in patients with newly diagnosed nonvalvular AF was associated with an increased risk of mortality (hazard ratio, 1.21 [95% CI, 1.17-1.25]; $P < .001$). Although the authors noted that their observational findings could be subject to confounding despite their use of propensity matching, nevertheless, partly on the basis of the results of this study, the use of digoxin for heart rate control in AF fell into disfavor.

Kotecha and colleagues[2] have conducted the first randomized clinical trial (Rate Control Therapy Evaluation in Permanent Atrial Fibrillation) comparing low-dose digoxin with the β-blocker bisoprolol for heart rate control in patients with permanent AF. In this open-label trial, 160 patients were randomized to receive digoxin at a mean dose of 161 µg/d (80 patients) or bisoprolol at a mean dose of 3.2 mg/d (80 patients). After 6 months, the primary end point of patient-reported quality of life (measured by the 36-Item Short Form Health Survey physical component summary score; range, 0-100; higher score is better) had a mean score of 31.9 (SD, 11.7) in the digoxin group vs 29.7 (SD, 11.4) in the bisoprolol group ($P = .28$). At 12 months, 8 of 20 secondary outcomes differed between the 2 groups (all favoring digoxin), including N-terminal pro-brain natriuretic peptide level, which was lower in the digoxin group (960 pg/mL) than in the bisoprolol group (1250 pg/mL) ($P = .005$). There was no significant difference in resting heart rate between the 2 groups at 12 months (mean of 75.4/min in the digoxin group vs mean of 74.3/min in the bisoprolol group).

On the basis of these results, low-dose digoxin may be considered a viable alternative to β-blockers to safely achieve heart rate control in patients with permanent AF. The relatively low dose of digoxin (mean, 161 µg/d) proved to be sufficient for heart rate control while avoiding the threat of digoxin toxicity. Because this trial was small and open label in design, the results may not markedly change the current clinical practice guidelines for heart rate control in AF. Still, among patients with permanent AF who do not tolerate β-blockers or calcium channel blockers, or who do not adequately respond to these drugs, digoxin may be useful to consider as a second-line agent.

A classic therapeutic intervention that had its beginnings over 2 centuries ago with the work of a physician in Birmingham has now been renewed by the work of a new generation of Birmingham physicians. With further research[6] to confirm and extend the results of Kotecha et al,[2] digitalis glycosides may once again find a valuable, albeit ancillary, place in the therapeutic armamentarium for treatment of patients with AF.

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