EDITORIAL COMMENT

Digoxin for Worsening Chronic Heart Failure
Underutilized and Underrated*

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Despite more than 200 years of clinical experience and a pivotal trial, digoxin, a purified cardiac glycoside derived from the foxglove plant, remains the most controversial drug in contemporary cardiovascular medicine (1,2). Although the U.S. Food and Drug Administration approved digoxin in 1997, the guidelines currently offer only a secondary recommendation (i.e., class IIa) for digoxin in: 1) patients with HF with reduced ejection fraction (EF) experiencing persistent symptoms despite optimal medical therapy; and 2) as an adjunct for rate control in patients with atrial fibrillation already receiving β-blockers and/or calcium channel blockers (3). However, there have been no major advances in the management of patients hospitalized for worsening chronic HF, and these patients remain at high risk for early readmission or death despite available therapies. Thus, there are compelling public health reasons to reconsider the use of digoxin, a drug that is known to improve signs and symptoms of congestion as well as reduce HF-related hospitalizations and readmissions.

This issue of JACC: Heart Failure features 2 observational studies exploring real-world practice patterns with digoxin therapy and digoxin toxicity. In the first study, Patel et al. (4) utilized data from the American Heart Association’s Get With The Guidelines–Heart Failure program to assess temporal trends and clinical characteristics associated with digoxin use at discharge among patients admitted for a primary diagnosis of HF. Between January 2005 and June 2014, digoxin prescription rates at discharge declined from 33.1% to 10.7% in patients with HF with reduced EF. Similarly, among patients with HF with preserved EF, digoxin use decreased from 16.0% to 5.7% over the same timeframe. As might be expected, digoxin prescription was associated with a history of atrial fibrillation and other high-risk clinical features. The authors appropriately acknowledge that these findings cannot be generalized to outpatients with HF and that an unknown proportion of patients may have had undocumented contraindications, intolerances, or drug–drug interactions that may have impacted clinical decision making.

In the second study, Hauptman et al. (5) performed a retrospective analysis of the Premier database describing the management of digoxin toxicity and clinical outcomes in the modern era. Of 28.5 million hospitalizations over nearly 5 years, only 24,547 admissions for digoxin toxicity were identified based on International Classification of Diseases-Ninth Revision coding for digoxin immune fab (DIF). The authors found that DIF was administered in 20%...
of patients, and most patients (i.e., 78%) received DIF within 1 to 2 days of admission. In addition, cardiovascular specialists were more likely than generalist physicians to treat with DIF, and the use of DIF was associated with emergency admission, arrhythmias, and acute renal failure/hyperkalemia. Notably, among patients with digoxin toxicity, there was no difference in mortality during hospitalization or length of stay based on DIF treatment status. Weaknesses of the study include the absence of objective clinical findings (i.e., symptoms, physical examination, electrocardiogram, and so on) and digoxin levels to corroborate the diagnosis of digoxin toxicity as well as the lack of post-discharge outcomes.

Why has the use of digoxin declined precipitously? The safety of digoxin was first challenged in the 1970s on the basis of several retrospective analyses suggesting digoxin therapy might be associated with increased mortality (6). This prompted the design and conduct of 3 prospective, multicenter, randomized, double-blinded, placebo-controlled trials: PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin) (7), RADIANCE (Randomized Assessment of [the effect of] Digoxin on Inhibitors of the Angiotensin-Converting Enzyme) (8), and the pivotal National Institutes of Health-sponsored DIG (Digitalis Investigation Group) (9) trials. In aggregate, these landmark studies provide a strong evidence basis for the efficacy and safety of digoxin therapy. In patients with HF with reduced EF, digoxin augments cardiac output (CO) and reduces pulmonary capillary wedge pressure without inducing potentially hazardous increases in heart rate or decreases in blood pressure (10,11). In addition, digoxin therapy improves signs and symptoms of HF and functional status (7,8). Similarly, digoxin reduced the incidence of all-cause, cardiovascular-related, and HF-specific hospitalizations in the DIG trial, which enrolled 6,800 stable ambulatory HF patients with an EF <45% (9). Interestingly, in the DIG ancillary trial, which enrolled 988 outpatients with HF with an EF >45%, digoxin use was associated with a trend towards a reduction in hospitalizations for worsening HF, which approached, but did not reach, the threshold for significance, perhaps in part due to the smaller sample size and reduced statistical power (12). Although digoxin is known to have a narrow therapeutic window, the absolute incidence of digoxin toxicity is low, both in the controlled setting of a clinical trial (9) and in the context of everyday practice (13,14). For example, in the DIG trial, the incidence of hospitalization for suspected digoxin toxicity was 2-fold higher in digoxin-treated patients, yet the rate was low overall (i.e., 2.0% vs. 0.9%) (9).

Although no overall survival benefit was observed in the DIG trial, the effect of digoxin on the mode of death is intriguing. In essence, a bidirectional effect was observed: a decrease in mortality due to progressive pump failure that was offset by an increase in death due to other cardiovascular causes (9). However, secondary analyses of the DIG database have raised the hypothesis that digoxin may improve survival in pre-specified high-risk subgroups including patients with New York Heart Association functional class III or IV symptoms, an EF <25%, and/or a cardiothoracic ratio >55% (15). Similarly, although there were initially concerns on the basis of retrospective analyses of the DIG trial that digoxin might increase mortality in subsets of patients at risk for digoxin toxicity such as women, the elderly, and patients with renal insufficiency, any potential detrimental effects on mortality are no longer significant after adjusting for serum digoxin concentration (16–18). In fact, a comprehensive post hoc analysis including all patients enrolled in the DIG main and ancillary trials found that digoxin use among patients with a SDC <1 ng/ml was associated with a robust survival benefit that was consistent across age, sex, EF, and comorbid disease states (16). As a result, the guidelines have been revised since the completion of the DIG trial and currently recommend a lower therapeutic SDC for HF (i.e., <1.0 ng/ml) (3). More recently, the peer-reviewed published reports and the popular press have highlighted a number of studies showing potential harm with digoxin therapy in both HF and atrial fibrillation. Notably, 2 independent research teams using different statistical methods performed secondary analyses of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) database and reached diametrically opposed conclusions regarding the effect of digoxin on mortality (19,20). This highlights the inherent limitations of secondary analyses, demonstrating that even with sophisticated statistical modeling, it may not be possible to comprehensively adjust for disease severity and the indication for treatment. In addition, these studies are based on prevalent digoxin use, and substantial differences in clinical characteristics may have emerged in the intervening time between drug initiation and data acquisition. Thus, although existing and future observational datasets may provide useful information regarding the epidemiology and real-world practice patterns with digoxin, definitive conclusions regarding its safety based on post hoc analyses should be interpreted with extreme caution (2).

In conclusion, there have been no major advances in the pharmacological management of patients
hospitalized for worsening chronic heart failure over the last 2 decades. These patients remain at high risk for early readmission or death (21,22). However, digoxin has multiple favorable properties that make it an ideal therapy for worsening chronic HF (23).Digoxin is the only available inotropic known to increase CO and decrease pulmonary capillary wedge pressure without causing deleterious increases in heart rate or decreases in blood pressure. In addition, digoxin improves signs and symptoms of HF and functional status. Digoxin is known to reduce all-cause and HF-specific hospitalizations. At SDCs <1 ng/ml and in certain high-risk groups, digoxin may improve survival. Accordingly, digoxin should be considered in patients with HF with reduced EF who remain symptomatic despite optimal medical therapy.

REFERENCES


KEY WORDS digoxin, heart failure, mortality, outcomes, readmissions

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