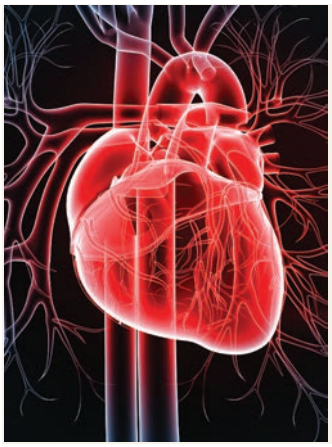

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HEARTBEAT

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Rehabilitation of Digoxin—Underutilized and Underrated

Digoxin is the oldest (200 years) cardiac drug still in contemporary use, yet its role in the management of patients with heart failure (HF) and/or atrial fibrillation (AF) remains controversial. Digoxin, a purified cardiac glycoside derived from the foxglove plant, increases left ventricular ejection fraction (LVEF), augments cardiac output (CO), and reduces pulmonary capillary wedge pressure (PCWP) without causing deleterious increases in heart rate (HR) or decreases in blood pressure (BP). It decreases atrial-ventricular conduction and decreases ventricular response in AF. Moreover, it also is a neurohormonal modulator at low doses. The use of digoxin has declined in recent years.[1] In this *Heartbeat,* we'll make a case to reconsider the role of digoxin in managing patients with heart failure (HF) and/or atrial fibrillation (AF).

Underutilization

Why has the use of digoxin declined precipitously? Perhaps it was overemphasis of the message (no decreased mortality) that led to underutilization of digoxin. Possibly physicians were concerned about polypharmacy that is involved in treating HF patients aggressively, and therefore decided to eliminate digoxin. Or maybe it was assumed that the morbidity benefit would be negligible once ACE inhibitors and beta-blockers were available for treatment of HF. (The DIG trial predated the use of ACE inhibitors and beta-blockers in most patients with HF.) One could even speculate that since digoxin is a low-cost generic medication, the lack of advertising may have played a role in forgetting the substantial non-mortality benefit and improvement in quality of life (reduced hospitalization). For whatever reason, many physicians don't use digoxin as part of their treatment program for systolic HF.

The safety of digoxin was challenged in the 1970s on the basis of several retrospective analyses suggesting digoxin therapy might be associated with increased mortality.[2] This prompted three prospective, multicenter, randomized, double-blind, placebo-controlled trials: PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin,[3] RADIANCE (Randomized Assessment of [the effect of] Digoxin on Inhibitors of the Angiotensin-Converting Enzyme)[4] and the pivotal National Institutes of Health–sponsored DIG (Digitalis Investigation Group) trials.[5] All of these studies provide evidence for the safety and efficacy of digoxin. The landmark DIG trial reduced the risk of hospitalization due to HF by 28% during 37 months (average) of follow-up without a significant effect on mortality.

Secondary analyses of the DIG database 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, a LVEF <25%, and/or a cardiothoracic ratio >55%.[6] Initially, there were 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. But potential detrimental effects on mortality were no longer significant after adjusting for serum digoxin concentration (SDC).[7,8] 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, LVEF and comorbid disease states,[9] resulting in a revision of the guidelines.

Digoxin: Friend or Foe?

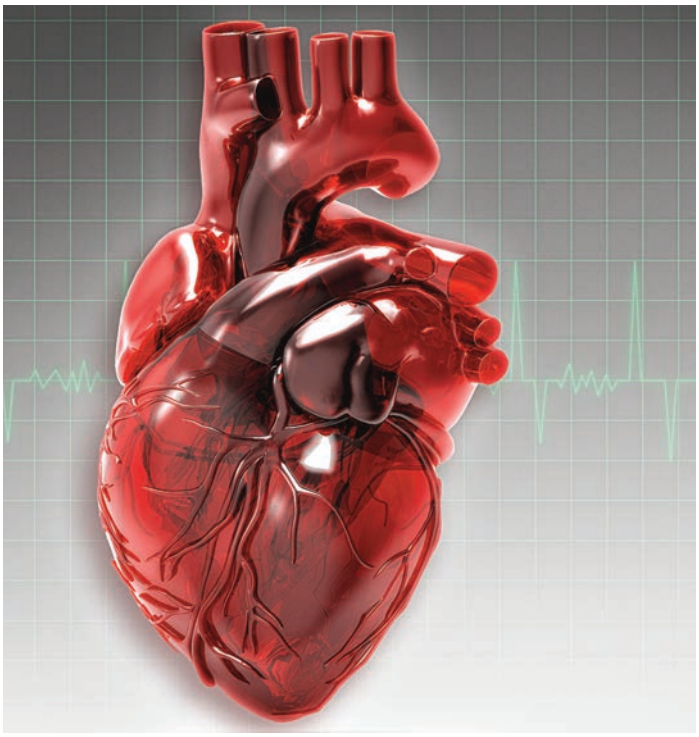
Starting at about the turn of the century, the use of digoxin has declined, partially because of concerns about safety. Recent cohort studies and meta-analyses of observational data have suggested that digoxin is associated with increased mortality. Even with the use of statistical adjustment and propensity matching, it is unclear whether observational data should be considered reliable in the context of decisions on pharmacotherapy, particularly as digoxin is conventionally prescribed to sicker patients. Indeed, the largest randomized controlled trial of digoxin in HF (DIG trial) showed neutral effects on mortality and a reduction in admissions to the hospital compared with placebo.

In a recent post hoc analysis of the DIG trial, Ahmed and colleagues tested the effect of digoxin on 30-day, all-cause hospital admission in ambulatory older adults (n = 3,405) with reduced LVEF who were randomly assigned to digoxin or placebo.[10] The study population was well treated, with more than 90% on ACE inhibitors and more than 80% on diuretic therapy. In this group of older patients, digoxin reduced the risk of 30-day all-cause hospitalization by 34% (5.4% vs. 8.1%; p = 0.002), 30-day hospitalization due to CV causes by 47% (3.5% vs. 6.5% for placebo; p < 0.001), and 30-day hospital admission due to worsening HF by 60% (1.7% vs. 4.2%; p < 0.001). Consequently, the composite outcome of all-cause hospitalization or all-cause death at 30 days also was reduced by 31%. (6.0% vs. 8.7%; p = 0.003). Thirty-day, all-cause CV mortality and progressive HF did not differ between groups, and the effect of digoxin persisted at both 60 and 90 days after randomization, suggesting that the early benefit of digoxin was not at the expense of later harm.

Results of several smaller randomized trials were consistent with the DIG findings, showing that digoxin improves symptoms and prevents clinical deterioration. For AF, however, no such experimental trials exist, and confusion about whether digoxin is truly linked to adverse prognosis led to the downgrading of digoxin in the guidelines.

Further Analysis Sheds Light on Discrepancy

To better understand the safety and efficacy (or lack thereof) of digoxin, a comprehensive literature search including all studies published from 1960 to July 2014 examined treatment with digoxin compared with control (placebo or no treatment).[11] Digoxin was associated with a small but significant reduction in-all cause hospital admission across all study types (overall risk ratio: 0.92; 95% CI: 0.89 0.95; p < 0.001), as well as significantly lower rates of admissions related to CVD (overall risk ratio: 0.92; 95% CI: 0.86-0.97) and HF (overall risk ratio: 0.89; 95% CI: 0.85-0.93). The authors comment their review sheds light on the discordant findings between the randomized and observational studies, adding, "They show that the mechanism of the association with mortality in observational studies is that clinicians preferentially gave digoxin to sicker patients: when these patients died, there was therefore a true but misleading association between death and digoxin."



In the accompanying editorial, the point Cole and Francis is making is apparent in their title: *Trials Are Best, Ignore the Rest.*[12] They point out that nearly 20 years after the DIG trial showed that digoxin reduced hospital admissions for HF by 28% with no effect on mortality, many clinicians still see this drug as a last resort; this is reflected in guidelines that reserve it for those with severe or worsening HF when first- and second-line treatments have failed.

A brand new retrospective analysis presented at the Heart Failure Society meetings concluded that digoxin didn't seem to seem to help the patients clinically and may have harmed them by raising the risk of readmission.[13] Unfortunately, this is another observational study. One limitation of the current analysis, in fact of many analyses of outcomes associated with digoxin for HF, is a lack of information about patients' levels, according to Dr. Paul J. Hauptman (Saint Louis University School of Medicine, St. Louis, MO). "The therapeutic range for SDC should be below 0.9 ng/mL for safety", said Dr. Hauptman, who wasn't involved in the current analysis. He's "pretty convinced," he said, "that a lot of patients who show adverse effects from digoxin in the literature have digoxin levels that are too high."

Hauptman and coauthors recently reported that 93% of 60 laboratories at top-rated U.S. hospitals that responded to their questionnaire considered SDC exceeding 2.0 ng/mL or higher as being in the "normal" range[14] — despite DIG data suggesting no benefit from levels higher than 0.9 ng/mL and possible harm at levels higher than 1.2 ng/mL. "We find that the 0.5 to 0.8 [ng/mL] is the sweet zone, 0.9 to 1.1 [ng/mL] is neutral, and at greater than 1.1 [ng/mL] there is increased mortality," writes Dr. Hauptman, emphasizing that he is referring to digoxin use in HF, not necessarily AF.

Presently, the guidelines offer only a secondary recommendation (i.e., class IIa) for digoxin in: 1) patients with HF with reduced LVEF experiencing persistent symptoms despite optimal medical therapy and 2) as an adjunct for rate control in patients with AF already receiving beta-blockers and/or calcium-channel blockers.[15]

Systematic review suggests that digoxin should continue to be considered as a treatment option to avoid hospital admissions in patients with HF and to achieve heart rate control in those with AF.

Conclusion

HF is the leading cause of hospital admission and readmission in the United States. These patients remain at high risk for early readmission or death despite available therapies. 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 *(for which hospitals are not getting paid and soon doctors won't)*. Digoxin has multiple favorable properties, which makes it an ideal therapy for chronic HF.[16] It is the only available inotrope known to increase CO and decrease PCWP without increasing HR or decreasing BP. In addition, it improves signs and symptoms of HF and functional status and is known to reduce all-cause and HF-specific hospitalizations. At SDC of 0.5-0.8ng/ml and in certain high-risk groups, digoxin may improve survival (neurohormonal effects). We think that *digoxin should be considered in patients with HF with reduced EF* who remain symptomatic despite optimal medical therapy. For our patients with AF *and difficult to control ventricular response we use low-dose digoxin in combination with beta-blockers and/or rate-limiting calcium-blockers.*

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