

## The Evolution of Digoxin in Heart Failure and Atrial Fibrillation: An Update in Role, Dosing, and Toxicity

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### Abstract

Digoxin has been recognized as a time-old therapy in cardiovascular medicine and its use has persisted in heart failure (HF) and atrial fibrillation (AF). However, whether digoxin is beneficial or harmful is still debated with a long history of conflicting data regarding the association between digoxin use and mortality in these patient populations. Recent studies on the impact of digoxin on clinical outcomes in observational and randomized controlled trials clarify the role and expectations of digoxin and the importance of digoxin levels in various clinical scenarios. Digoxin with dosing maintained at 0.5 - 0.8 ng/mL is recommended in the setting of HF with reduced ejection fraction (HFrEF) with normal sinus rhythm, particularly in NYHA class III-IV, LVEF < 25%, or cardiothoracic ratio (CTR) > 55% for symptomatic improvement and to decrease hospitalizations for heart failure exacerbations, as an adjunct to goal directed medical therapy. In AF patients already on long term digoxin, therapy should be continued at dosing < 1.2 ng/mL, otherwise initiation of digoxin therapy is not favored. In both patient subsets, periodic serum digoxin concentration (SDC) monitoring is important especially in those at risk for labile levels. With the use of digoxin, toxicity remains a risk and digoxin-specific antibody fragments (DIF) may begin to be used more liberally. Hence, this paper reports and evaluates the changing data surrounding this drug and addends its use in clinical practice.

**Keywords:** Heart Failure; Atrial Fibrillation; Risk; Therapy; Dosing; Toxicity

### Introduction

Since its inception by Withering from the foxglove plant in 1785 digoxin has received attention for its attractive therapeutic effects and pharmaceutical potential [1]. However, its clinical use has continued to wax and wane in the setting of its narrow therapeutic window and its questionable correlation with mortality. From its origin as a mainstay treatment in heart failure digoxin has since revived its role in contemporary medical therapy of systolic heart failure and additionally raised questions of its role in atrial fibrillation (AF).

### Heart Failure with sinus rhythm

Digoxin lost favor until 1997 when the DIG trial elucidated its role in heart failure and resurrected the medication in clinical practice. In the large randomized trial digoxin proved its worth in reducing hospitalizations with no impact on mortality in HFrEF patients with normal sinus rhythm [2]. Its clinical use was addended shortly after with the return of serum digoxin level monitoring, the cumbersome practice once standard of care due to fear of toxicity and a factor that ultimately led to its initial demise as a medication of choice. *Post hoc* analysis of the DIG trial revealed low SDC is optimal and a goal of 0.5 - 0.8 ng/mL has since been established [3-5]. The reciprocal increase in hospitalization without an increase in mortality was demonstrated when long term digoxin therapy was discontinued as expected, leading to the follow up recommendation to continue these patients on digoxin at the low SDC [6]. Further impressions of digoxin came more recently with a post follow up analysis of the DIG trial in which more significant improved outcomes were seen in high risk subgroups of HFrEF patients defined as NYHA class III-IV, LVEF < 25%, or CTR > 55%. However, HF mortality and HF hospitalization were

combined endpoints and thus the clarity of digoxin's effect on outcomes achieved in the DIG trial is not present here. Despite this lack of clarity, significant improvement in outcomes cannot be denied and has led to further emphasis of adding digoxin to HF regimen in these high risk HFrEF patients [7].

### Atrial Fibrillation with and without heart failure

Evaluation of digoxin in atrial fibrillation has heightened within the last decade following the emergence of rate control as opposed to rhythm control in the AFFIRM trial in 2002. As rate control matched rhythm control in survival amongst AF patients [8], digoxin in the rate control arm gained attention and provoked further *post hoc* analyses and observational studies. Its clinical outcomes in AF with and without CHF has been elusive due to conflicting results and the absence of a randomized outcomes trial such as exists for heart failure. A number of these studies have shown an association between digoxin and all-cause mortality [9-15] while others are in direct contradiction having concluded a neutral effect [16-20], with two conflicting meta-analyses amongst them. The dichotomy in results has been attributed to not only the setting of observational studies but more importantly the lack of digoxin serum concentration (DSC) data. With these limitations the question of causality remains especially with prominent confounders such as heart failure.

A new study, contending to be the largest and most comprehensive analysis to date, presented at the ACC 66<sup>th</sup> Annual Scientific Session in March, 2017 brings us closer to elucidating the association between mortality and digoxin in AF patients and more importantly preliminarily dictates against its use in AF regardless of CHF until a randomized trial may be performed. The study used data collected in the ARISTOTLE trial with propensity matched analyses and is the first of its kind to examine DSC in AF. In patients already receiving digoxin, risk of death was related to serum concentrations with significance when levels were greater than 1.2 ng/ml. This study also reports increased risk of mortality with initiation of digoxin in digoxin naïve AF patients [21] in agreement with findings in the TREAT-AF trial [13], the only two studies for which this is evaluated.

### Digoxin serum concentration and toxicity

As mentioned previously the narrow therapeutic window with high risk of toxicity (> 2 ng/mL) has stifled the pharmaceutical utility of digoxin from the beginning. Digoxin is widely distributed in body tissues with blood levels dependent on body weight, age, renal function, concomitant drugs, and concurrent disease. The seeming importance of SDC warranted the practice of SDC monitoring and has since commanded scrutiny for years with continued fluctuation in thought. In light of evidence of optimal therapeutic ranges in both HF and AF as discussed above, the pendulum has swung back in favor of monitoring the levels.

For initiation of therapy a loading dose may be given and a SDC obtained after 12 - 24 hours to examine the response but is usually of minimal value in establishing maintenance dosing. In the absence of a loading dose the DSC should be obtained after 3 - 5 days of therapy. When monitoring maintenance therapy, trough concentrations just prior to the next dose or 6 - 8 hours after the last dose should be followed. After any dosage change, DSC should be evaluated after time to steady-state, typically 5 - 7 days but may be longer in the setting of renal impairment reaching up to 15 - 20 days in ESRD [22].

The pharmacology of digoxin subjects SDC to electrolyte sensitivity and therefore closer monitoring is recommended in renal dysfunction (especially changing renal function), electrolyte depleting medications (diuretics), or history of electrolyte disturbances (hypokalemia or hypomagnesemia). Additionally digoxin demonstrates significant drug-drug interactions, most notable for CHF and AF patients are amiodarone, quinidine, and verapamil along with commonly prescribed macrolide antibiotics. Thus, initiation or discontinuation of medications merit obtaining a DSC. Other indicators for measuring DSC include clinical deterioration, any disease changes (thyroid disease), or suspected toxicity [22].

Toxicity remains the feared complication of using digoxin in the clinical setting with only a seemingly loose downtrend in incidence over the last decade. Though the most common manifestation of digoxin toxicity is nausea and vomiting, other manifestations of toxicity

may include anorexia, visual disturbances, and confusion [23]. Electrocardiographic manifestations are of particular concern and range from ventricular premature complexes (VPCs) most commonly to bradyarrhythmias, junctional tachycardia, paroxysmal atrial tachycardia with variable block, and bidirectional ventricular tachycardia [24]. Contemporary data was presented by Hauptman et al in a retrospective study using a national hospital database. Annual toxicity admissions decreased from 2007 to 2011 with an incidence of 2.4% of hospitalized HF and AF in 2011 and a predominance in the elderly specifically age 85 years or older [25]. Treatment of toxicity using digoxin-specific antibody fragments (DIF) has proven safe and effective and is recommended for life threatening poisoning presenting with bradyarrhythmias, ventricular arrhythmias, hyperkalemia > 6 mmol/L, or hemodynamic instability with elevated DSC > 2.6 mmol/L [26]. Despite limited indications, Hauptman et al found DIF was administered in 20% of toxicity within 2 days of hospitalization. Although no difference in mortality or length of stay was significant when compared to patients not receiving DIF, prospective data is needed to establish these clinical outcomes [25]. The recommendations have largely been dictated by cost restraints and is thus changing with the advent of reduced dosing, with evidence for 80 mg and 40 mg repeat boluses in acute and chronic toxicity, respectively [26]. Megarbane and Baud suggest encouraging more liberal administration of DIF to improve outcomes for non life-threatening toxicity [27].

### Conclusions

In regards to HF, digoxin use secondary to goal-directed medical therapy is recommended in HFrEF with normal sinus rhythm [28,29], particularly in NYHA class III-IV, LVEF < 25%, or CTR > 55% for symptomatic improvement and to decrease hospitalizations for HF exacerbations. Dosing should be maintained at 0.5-0.8 ng/mL with DSC monitoring.

In regards to AF, digoxin use remains difficult. It is not recommended as a first line therapy for rate control in AF. However, it has been considered in combination with a beta blocker and/or non-dihydropyridine calcium channel blocker when the ventricular rate is poorly controlled in patients with underlying left ventricular dysfunction [30,31]. With most recent studies suggestive of risks outnumbering the benefits particularly with initiation therapy, use of digoxin in AF may best be approached by differentiating the patient population by exposure. In AF patients already on long term digoxin, data suggests continuation of therapy at lower DSC < 1.2 ng/mL with DSC monitoring. In digoxin-naïve AF patients most recent studies favor not initiating digoxin therapy.

According to the most recent guidelines, periodic monitoring is explicitly recommended in AF but is less clear in HF as monitoring for toxicity is recommended [28-31]. Given the low DSC parameters in both CHF and AF it seems reasonable to recommend periodic monitoring in both HF and AF patients on digoxin therapy. In patients with heightened risk of labile digoxin levels including increasing age, renal impairment, and susceptibility to electrolyte abnormalities, closer periodic monitoring is suggested.

With lower target therapeutic ranges, we may see a decline in the incidence of digoxin toxicity. However, high level of suspicion should be maintained and DIF used in life-threatening poisonings. Improvement in dosing may allow for more widespread use with earlier administration in the subset of patients felt to be at lower risk for toxicity.

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