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Contemporary Controversies in Digoxin Use in Systolic Heart Failure

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Abstract Digoxin remains one of the oldest therapies for heart failure; however, its safety and efficacy have been controversial since its initial use. Questions that remain include the clinical efficacy of digoxin when added to contemporary medical therapy, when and if it should be added, and how to minimize adverse effects. In this review, we will summarize recent data on the use of digoxin in systolic heart failure and address some of the controversies regarding the role of digoxin in the modern era of heart failure treatment.

Keywords Digoxin · Heart failure

Introduction

Digitalis, a cardiac glycoside derived from the purple foxglove plant (*Digitalis lanata* and *Digitalis purpurea*), was initially reported for the treatment of heart failure by Withering in 1785 [1]. While digoxin, a pharmaceutically purified version of digitalis, remains one of the oldest treatments for heart failure, its role remains fraught with controversy. Since the Digoxin Investigators Group (DIG) trial in 1997, there has not been another randomized clinical trial of digoxin in the modern era of heart failure management [2]. Questions that remain include what is the clinical efficacy of digoxin when added to contemporary medical therapy, when and if it should be added, and how to minimize adverse effects. We will review the current society guidelines as well as summarize recent trials and publications on the use of digoxin in systolic heart failure that address the current controversies.

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Mechanism of Action

Digoxin works via several mechanisms to produce its salutary effects on the heart [3–5]. Digoxin binds to the alpha subunit in the membrane sodium-potassium ATPase channel and blocks the efflux of sodium (Fig. 1). The reduction of sodium efflux then lowers the sodium gradient needed for calcium efflux through the sodium-calcium exchanger channel, thereby increasing intracellular calcium. Increased intracellular calcium is stored within the sarcoplasmic reticulum via the SERCA2A channel. At the level of the cardiomyocyte, the increased release of calcium from the sarcoplasmic reticulum leads to increased contractility via enhanced sarcomeric excitation-contraction coupling. Thus, digoxin works as a positive inotrope.

Digoxin lengthens the cardiac action potential, specifically phase 0 and 4, which leads to reduction in heart rate. Digoxin suppresses sympathetic tone by increasing the sensitivity of the baroreceptors while also increasing parasympathetic tone. Importantly, it also reduces neurohormone levels including norepinephrine, plasma renin, and aldosterone.

Hemodynamic and Symptomatic Impact of Digoxin in Heart Failure

Several early studies evaluated the short-term hemodynamic effects of digoxin in systolic heart failure. Using right heart catheterization and administration of 1 mg of IV digoxin, these studies consistently demonstrated an acute improvement

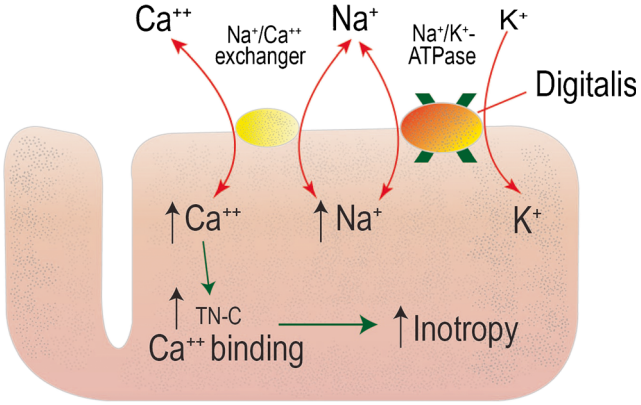

Fig. 1 The mechanism of digoxin in the cardiomyocyte

in cardiac output, a decrease in pulmonary capillary wedge pressure, an increase in ejection fraction, and a varied response in systemic vascular resistance [6–9]. It is important to note that the most significant response was found in those with worse baseline hemodynamics and lower ejection fraction. These hemodynamic changes translated clinically into improved heart failure symptoms, exercise tolerance, and peak oxygen consumption. [10–18].

Guideline Recommendations

The current society guidelines are largely driven by the results of the DIG trial. The AHA/ACCF Heart Failure Guidelines recommend the addition of digoxin to standard goal-directed neurohormonal therapy in patients who have persistent heart failure symptoms. Also, in those who are already on digoxin, it is not recommended to withdraw it when initiating other goal-directed medical therapy for heart failure. Digoxin is given a class IIa, level of evidence C recommendation for patients with reduced ejection fraction to reduce hospitalizations, unless contraindicated [19].

The European Society of Cardiology has similar recommendations for the use of digoxin in systolic heart failure but has decreased the recommendation strength over the years. They specify that digoxin should be considered to reduce heart failure hospitalizations in patients with an ejection fraction less than 45 % and in sinus rhythm who cannot tolerate beta-blockers. Additionally, these patients should be receiving other goal-directed medications such as ACE inhibitors or ARBs and MRAs. Digoxin can also be considered in patients on beta-blockers who have persistent symptoms. Both of these recommendations are class IIb, level of evidence B [20].

Dosing, Levels, and Monitoring of Digoxin in Heart Failure

Digoxin is available in oral (tablet or liquid formulations), intramuscular (IM), or intravenous (IV) formulations. Loading doses can be given either intravenously or orally, noting that the oral bioavailability is about 75–80 %. Maintenance dosing is generally 0.125 to 0.25 mg daily. The dose should be adjusted depending on renal function, lean muscle mass, and concomitant medications that may cause an increase in serum levels. While a loading dose may be used to achieve immediate effects, particularly in atrial fibrillation with rapid ventricular response, it is not recommended when used in the management of chronic systolic heart failure.

Given the long half-life of digoxin (approximately 36 h), steady state is achieved in about 5–7 days, and even longer in patients with impaired renal function. When checking digoxin levels, it should be done at least 6 h after the last dose. The current guidelines do not make recommendations about monitoring of digoxin levels. Recent studies have identified that a narrower therapeutic window of 0.5–0.9 ng/mL improves mortality, while there is a trend toward worse mortality and morbidity in levels >1.1 ng/mL [21, 22]. Ahmed et al. performed a more recent post hoc analysis of the DIG trial including the ancillary trial and evaluated all patients who were alive 1 month post-randomization and had a serum digoxin level measured ($n = 5548$). After a median follow-up period of 40 months, they identified that patients with a serum digoxin concentration of 0.5–0.9 ng/mL had a relative risk reduction in all-cause mortality and heart failure hospitalization of 23 and 38 %, respectively, compared to patients randomized to placebo. For patients who had a serum digoxin level >1 mg/mL, there was still a 32 % relative risk reduction in heart failure; however, the mortality was comparable to patients who received placebo [23].

The older methods for digoxin dosing have been replaced by a new normogram that targets the narrower therapeutic window of 0.5–0.9 ng/mL, which incorporates creatinine clearance, ideal body weight, and height [24–28]. Digoxin has significant drug-drug interactions with several drugs, notably, amiodarone, quinidine, verapamil, and macrolide antibiotics.

Adjustments in Renal Failure

Since 50 to 70 % of digoxin is excreted unchanged in the urine, dosing adjustments are often necessary in patients with reduced creatinine clearance (CrCL) to maintain a therapeutic window and avoid toxicity [29]. In patients with end stage renal disease, the loading dose of digoxin should be reduced by 50 %, and a maintenance dose should be 10 to 25 % of the usual dose every 48 h. It should be noted that due to extensive binding to the skeletal muscle and myocardium, digoxin cannot be removed via dialysis. In patients with CrCl >60 mL/min, no dosage adjustment is necessary. For CrCL30-60 mL/min, the recommended dose reduction is 25 to 50 % of the usual dose (i.e., 0.0625–0.125 mg daily). For CrCl <30 mL/min, a recommended starting dose is around 0.125 mg every 48 h.

Trials and Studies

Early Digoxin Trials

Digoxin was approved by the FDA for the treatment of heart failure in 1998 and for control of ventricular rate in patients with atrial fibrillation. Several early trials paved the way for its approval including PROVED and RADIANCE, which were digoxin withdrawal studies.

In PROVED, a prospective, randomized, double-blind, placebo controlled multicenter trial, 88 patients with left ventricular dysfunction were randomized to digoxin continuation or withdrawal on a background regimen of diuretic and digoxin. The patients in the withdrawal group showed worsened maximal exercise capacity ($p = 0.003$), lower ejection fraction ($p = 0.016$), and increased incidence of heart failure exacerbations ($p = 0.039$) [11]. In RADIANCE, 178 patients with left ventricular ejection fraction (LVEF) of 35 % or less and New York Heart Association (NYHA) class II–III symptoms on a stable regimen of digoxin, diuretics, and an angiotensin-converting-enzyme inhibitor (captopril or enalapril) were randomized to withdrawal or continuation of digoxin for 12 weeks. There was a clinically significant increased rate of worsening heart failure, with a relative risk of 5.9 (95 % confidence interval 2.1–17.2) in the placebo group compared to the digoxin group. The patients switched to placebo from digoxin also had lower quality of life scores, ejection fractions ($p = 0.001$), increases in heart rate ($p = 0.001$), and body weight ($p < 0.001$) [30].

The DIG Trial

The Digitalis Investigation Group (DIG) trial, published in 1997, was the first large, randomized, double-blind placebo-controlled clinical trial of digoxin in ambulatory patients with systolic heart failure and normal sinus rhythm [2]. Patients with LVEF of 45 % or less were randomly assigned to digoxin ($n = 3397$) or placebo ($n = 3403$) in addition to standard background heart failure medications which, at the time the study was undertaken, included angiotensin-converting-enzyme inhibitors (94 % of patients) and diuretics (82 % of patients). The primary endpoint of the study was all-cause mortality, with the secondary endpoint being hospitalization for heart failure. All NYHA functional classes were included in the study, as long as patients met the LVEF <45 % criteria. In the cohort, 70 % of the patients had ischemic cardiomyopathy and 22 % were women. The median dose of digoxin was 0.25 mg per day, with mean serum digoxin level of 0.86 and 0.80 ng/mL at the 1 and 12-month visits. The average follow-up was 37 months.

There was no difference in mortality between the digoxin and placebo groups. The mortality was 34.8 % in the digoxin group and 35.1 % in the placebo group. However, there was a trend toward decreased deaths attributed to worsening heart failure in the digoxin group (risk ratio, 0.88; 95 % confidence interval, 0.77–1.01; $p = 0.06$) (Fig. 2). Importantly, there was a significant reduction in hospitalizations for worsening heart failure in the digoxin group (risk ratio 0.72; 95 % confidence interval 0.66 to 0.79; $p < 0.001$) (Fig. 3). Thus, the DIG trial suggested a role for digoxin in reducing heart failure hospitalizations, with a trend toward reduction in mortality from worsening heart failure.

DIG Trial Subgroup and Post Hoc Analyses

The data set collected for the large, randomized DIG trial have been utilized for a number of post hoc analyses to further understand the impact of digoxin in heart failure. A subgroup

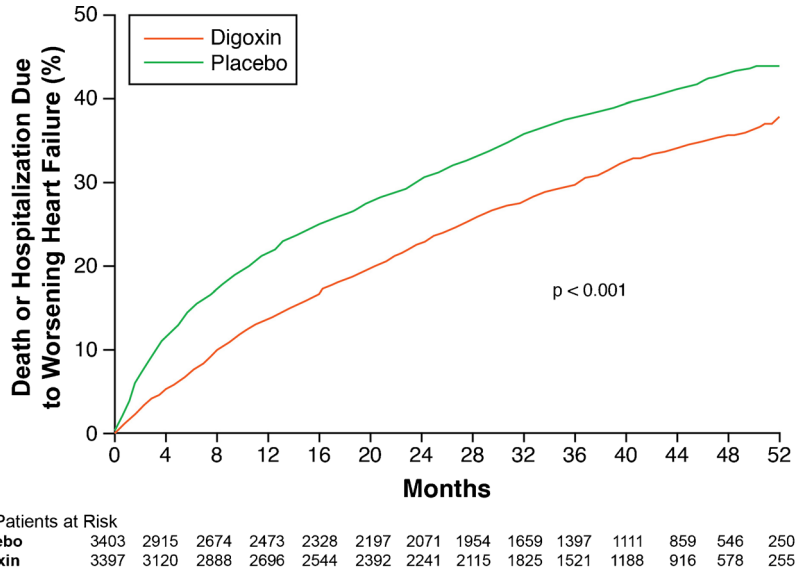

Fig. 2 In patients randomized to treatment with digoxin, there was a significant decrease in the combined endpoints of death from heart failure and hospitalization for heart failure (data from the DIG trial)

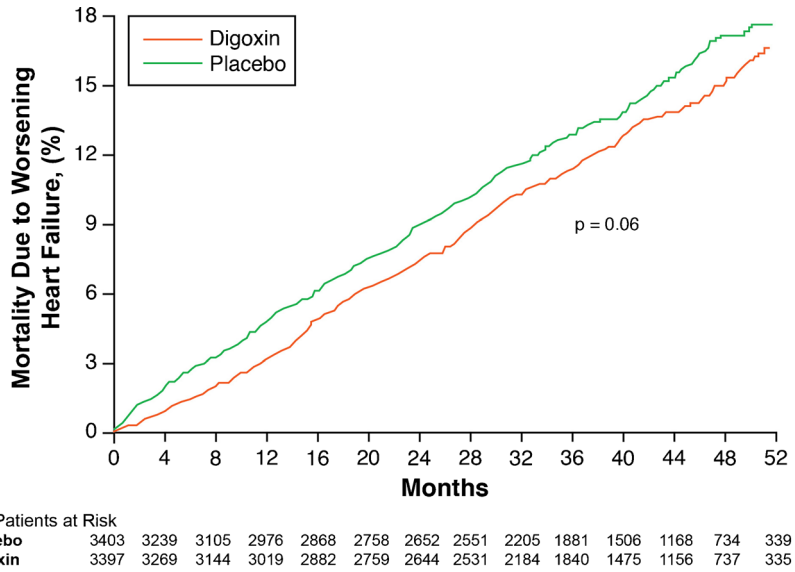

Fig. 3 In patients randomized to treatment with digoxin vs. placebo, there was no significant difference in mortality from worsening heart failure (data from the DIG trial)

analysis of the DIG trial evaluating pre-specified high risk groups defined as NYHA III–IV symptoms ($n = 2223$), LVEF <25 % ($n = 2256$), and cardiothoracic ratio >55 % ($n = 2345$) found that in all three high risk groups, digoxin was associated with lower 2 year all-cause mortality or all-cause hospitalization [31]. Digoxin use was also associated with a reduction in 30-day all-cause hospital admission in older ambulatory patients with chronic systolic heart failure [32]. In another subgroup analysis in which patients who had renal function assessed at baseline and 1 year ($n = 980$), randomization to digoxin was associated with improved renal function as defined by an increase of >20 % increase in estimated glomerular filtration rate (adjusted odds ratio 1.6; $p = 0.02$). In the group of patients with improved renal function, digoxin was also associated with significantly improved hospitalization free survival (adjusted HR 0.49, 95 % confidence interval 0.3–0.8; $p = 0.006$; p interaction $= 0.026$) [33].

Conversely, a cluster analysis of the DIG trial data using multivariate cox regression analysis suggests certain baseline characteristics were more often associated with worse outcomes when treated with digoxin (such as increased mortality or no reduction in heart failure hospitalizations). These baseline characteristics include higher ejection fraction, hypertension, diabetes, and female sex. In contrast, peripheral edema and S3 gallop were associated with significantly reduced heart failure admissions [34].

Digoxin Therapy and Sex-Based Differences

Several studies have examined sex-based differences in response to digoxin. A post hoc analysis of the DIG trial initially suggested that digoxin is associated with higher mortality in women but not men [35]. The interaction between sex and digoxin therapy was analyzed using Mantel-Haenszel tests of heterogeneity and a multivariable Cox proportional-hazards model, which was adjusted for demographic and clinical variables. Women randomized to digoxin had a higher rate of death then women randomly assigned to placebo (hazard ratio, 1.23; 95 % confidence interval, 1.02 to 1.47). In males, digoxin therapy was associated with a small, non-significant reduction in the risk of death from any cause (hazard ratio, 0.93; 95 % confidence interval 0.85–1.02). Additionally, women had a smaller digoxin-associated reduction in heart failure hospitalization then men. However, in another retrospective analysis of the DIG trial, serum digoxin concentration of 0.5–0.9 ng/mL in women was found to have a beneficial effect on mortality (hazard ratio 0.8, 95 % confidence interval 0.62 to 1.13) and for death or hospital stay for worsening heart failure (hazard ratio 0.75, 95 % confidence interval 0.58 to 0.930). Yet those women with a serum digoxin concentration from 1.2 to 2.0 ng/mL had an associated with a hazard ratio of 1.33 for death in women [36].

To further investigate the sex-based differences of digoxin in heart failure, Domanski et al. performed a post hoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD) [37]. SOLVD was a double-blind, randomized study of enalapril vs. placebo that enrolled 6797 patients with symptomatic or asymptomatic systolic heart failure with LVEF less than 35 %. Of all SOLVD patients, 1874 males and 370 females were treated with digoxin. In comparison to the female cohort, the male cohort was younger, largely white, with worse serum creatinine, less diabetes, and less diuretic use. There was no difference in all-cause mortality, or mortality attributable to cardiovascular, heart failure, or arrhythmic causes. Taken together, these studies do not suggest digoxin is harmful in women; rather, they urge increased caution in dosing female patients.

Contemporary Studies of Digoxin

As heart failure management has evolved over the last two decades to include therapies with mortality benefit such as beta blockers, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid antagonists, cardiac resynchronization therapy, and neprilysin inhibitors, more contemporary studies have been conducted to clarify the effect of digoxin in this new era. Though no randomized clinical trials have been conducted on the use of digoxin with these contemporary heart failure medications, many retrospective and prospective cohort studies have been done, with mixed findings.

In a single center, retrospective study of 347 male patients with systolic heart failure with left ventricular ejection fraction less than 45 %, Dahliwal et al. examined the effects of digoxin on all-cause mortality or readmission for heart failure [38]. At the time of this study, background heart failure (HF) therapy was considered to be angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker, beta-blocker, loop diuretic, hydralazine, long acting nitrates, and spironolactone. The digoxin patients and non-digoxin patients were prescribed similar regimen of heart failure medications, with some important exceptions; in the digoxin group, more patients were on a diuretic, fewer patients were on a beta-blocker, and fewer were on a statin. The patients who were prescribed digoxin were older, with lower LVEF (20 vs. 25 %), with more previous HF admissions, and were less hypertensive. This study did not detect a difference in survival or HF readmissions in this cohort.

The Valsartan Heart Failure Trial (Val-HeFT) was a randomized, placebo-controlled, double blind, multicenter trial of the angiotensin receptor blocker valsartan in patients with symptomatic heart failure with LVEF less than 40 % on a background therapy of angiotensin-converting-enzyme inhibitors, beta blockers, digoxin, and diuretics [39]. A post hoc analysis of the Val-HeFT study revealed that 67 % of patients were receiving digoxin therapy. After adjusting for baseline group differences including medical therapy and rhythm, digoxin use was still associated with higher all-cause mortality (HR 1.28; 95 % confidence interval 1.05–1.57), first morbid event defined as death, sudden death with resuscitation, or administration of intravenous inotropic or vasodilator drugs (HR 1.35; 95 % confidence interval 1.15–1.59), and heart failure hospitalization (HR 1.41; 95 % confidence interval 1.12–1.78) [40].

In the randomized aldactone evaluation study (RALES trial), which demonstrated a mortality benefit with the addition of spironolactone to background therapy for patients with heart failure with reduced ejection fraction of less than 35 %, a large portion of the patients were on digoxin background therapy at time of randomization in the trial (72 % of those receiving placebo and 75 % of patients randomized to spironolactone). The mortality benefit of spironolactone was only significant in patients already on digoxin therapy, while it was not significant in the 25 % of patients not taking digoxin [41].

In a prospective cohort study of patients between 2006 and 2008 in the Northern California Kaiser Permanente health system, Freeman et al. analyzed the association between incident digoxin use and the risks of death and heart failure hospitalization. Of 2891 patients newly diagnosed with systolic heart failure with LVEF less than or equal to 40 % who had no prior exposure to digoxin, 18 % received digoxin therapy during the study period. The patients treated with digoxin had lower prevalence of prior myocardial infarction, hypertension, and dyslipidemia, but a higher prevalence of atrial fibrillation and chronic lung disease. Of note, patients on digoxin therapy were also less likely to be treated at baseline with angiotensin-converting-enzyme inhibitors, loop diuretics, beta blockers, dihydropyridine calcium channel blockers, antiplatelet agents, and diabetes medications. Using multivariable extended Cox regression, the study found that digoxin use was associated with higher mortality (hazard ratio, 1.72; 95 % confidence interval, 1.25–2.36), but digoxin use was not found to have significant difference in the risk of heart failure hospitalization (hazard ratio, 1.05; 95 % confidence interval, 0.82–1.34). These associations of digoxin were seen regardless of sex or beta-blocker use. Interestingly, 30 % of patients on digoxin had no digoxin levels drawn during the study period [42].

Another large retrospective cohort study of 5153 Medicare beneficiaries with an index hospitalization for acute heart failure examined the role of digoxin at reducing 30-day all-cause readmission, heart failure readmission, and all-cause mortality. In this cohort, 20 % were discharged with a new prescription for digoxin. For patients with LVEF less than 45 %, digoxin was associated with significant reduction in 30-day readmission (HR 0.63; 95 % confidence interval 0.47–0.83), and this difference persisted throughout the first 12 months post-discharge. This benefit of digoxin was not found in patients with LVEF greater than 45 %. The hazard ratio for 12-month heart failure readmission was 0.72 (0.61–0.86) and for all-cause mortality was 0.83 (0.70–0.98) [43].

In a retrospective cohort study of 455 patients with advanced heart failure being evaluated for transplant, Gerogiopoulou et al. evaluated the role of digoxin with respect to the primary outcomes of death, urgent cardiac transplantation, and left ventricular assist device implantation. The cohort of patients had a mean age 52 ± 12 years with a mean LVEF 18.3 ± 8 %. The patients in this study were on an optimized heart failure regimen: beta-blockers (91.2 %), angiotensin-II modulation (92.5 %), aldosterone antagonist (45.6 %), and device therapy (71.0 %). After a median follow-up of 27 months, 36.6 % of patients treated with digoxin and 15.8 % patients treated without digoxin met the primary

outcome. Thus, no clear benefit was seen in this cohort of patients with advanced heart failure taking a contemporary regimen of heart failure therapies. However, it is very likely that digoxin use was a marker of disease severity in this population [44].

Though there has not been a large, multicenter, randomized clinical trial since the DIG and DIG ancillary trials, these more contemporary studies of digoxin demonstrate an unclear benefit to digoxin therapy in patients with systolic heart failure on a background of contemporary therapies for heart failure.

In Patients With Atrial Fibrillation and Heart Failure

Several studies have evaluated the effect of digoxin in patients with systolic heart failure and atrial fibrillation. AFFIRM was a randomized clinical trial of rate control vs. rhythm control strategy in patients with atrial fibrillation and a high risk for stroke. Several post hoc analyses have been performed from the AFFIRM registry to better understand the role of digoxin in this population of patients. Corley et al. found that digoxin was the only rate-control drug that was associated with an increased risk of death (HR 1.42), while beta-blockers and calcium channel blockers were effect neutral [45]. Another post hoc analysis of AFFRIM by Whitbeck et al. reported a similar association of digoxin with a higher all-cause mortality in atrial fibrillation (adjusted HR 1.41; 95 % confidence interval 1.19–1.67) [46]. However, in both of these studies, digoxin use was analyzed as a time-dependent treatment variable. This assumes that changes in treatment during the follow-up period occur in a random fashion. Gheorghiade et al. contend that changes in digoxin use over time cannot be assumed to occur at random, as these changes likely reflect clinical status, such as worsening heart failure symptoms. Thus, in a propensity-matched balanced cohort of patients in AFFIRM, Gheorghiade found that digoxin use had no association with mortality in patients with HF with reduced and preserved ejection fraction [47]. Furthermore, the AFFIRM trial protocol encouraged a digoxin level of >1 ng/mL, which is higher than the 0.5–0.8 ng/mL drug concentration previously found to lower mortality in the DIG post hoc analysis.

In a population-based, retrospective, cohort study of patients admitted to the hospital between 1998 and 2012 with a diagnosis of atrial fibrillation aged ≥65, Shah et al. examined the effect of digoxin on the risk of all-cause mortality in this population [48]. This cohort of patients was grouped into those with and without heart failure and into digoxin and non-digoxin treatment groups. Using a Cox proportional hazards regression analysis, digoxin was associated with 14 % greater risk of all-cause mortality in patients with heart failure (adjusted hazard ratio 1.14, 95 % confidence interval 1.10–1.17) compared to 17 % greater risk in patients without heart failure. However, it should be noted that the patients in this cohort were, on average, 80 years old, which is significantly older than populations studied in the previous trials.

Digoxin and Defibrillator Therapy

Because of the potential pro-arrhythmic effect of digoxin, two studies have examined the association of digoxin with defibrillator discharges and ventricular arrhythmias. Adelstein et al. evaluated 350 patients undergoing cardiac resynchronization therapy-defibrillator (CRT-D) implantation as primary prevention for ischemic cardiomyopathy with LVEF less than 35 %; 46 % of these patients received a prescription for digoxin at time of discharge from CRT-D implant. Over a mean follow-up of 48 months, digoxin therapy was associated with shorter time to first appropriate shock in intention-to-treat analysis (hazard ratio 2.18, 95 % confidence interval 1.27–4.05, $p = 0.007$). Overall survival and incidence of anti-tachycardia pacing were similar in patients on and off digoxin therapy. However, patients on digoxin had a lower baseline LVEF and were more likely to be on a loop diuretic and mineralocorticoid antagonist [49]. A post hoc analysis of the MADIT-CRT trial of patients with left ventricular function less than 30 %, NYHA class I or II symptoms, and QRS duration ≥130 ms found that while digoxin therapy was not associated with increased mortality or heart failure, digoxin was associated with a 41 % increased risk of ventricular tachycardia or fibrillation [50].

Meta-Analyses

Two recent meta-analyses have been carried out by Vamos et al. and Ziff et al. to further clarify the somewhat conflicting role of digoxin in the heart failure population. Vamos et al. culled 19 studies from 1993 to 2014 that analyzed the effects of digoxin on all-cause mortality, 10 of which studies were on patients with systolic heart failure, and 3 of which on patients with both atrial fibrillation and heart failure. They found that digoxin use was associated with an increase in mortality in all comers, but more so in patients with atrial fibrillation without heart failure, than in those with congestive heart failure [51].

Ziff et al. expanded the timeline to include studies from 1960 to 2014, with 52 studies analyzed with the primary endpoint of all-cause mortality, and all secondary endpoints, including hospital readmissions. They found that patients prescribed digoxin tended to be older, with lower ejection fraction, have an increased prevalence of diabetes, and to be taking more anti-arrhythmic medications than those in the non-digoxin cohort. This further suggests the role of prescription bias in the non-randomized digoxin trials. Even despite these differences, Ziff et al. concluded that digoxin was effect neutral in mortality but demonstrated reduction in hospital readmission [52].

Prescription Trends

Given that the efficacy of digoxin in the treatment of patients with systolic dysfunction remains somewhat controversial in literature, the prescription pattern for this medicine was studied in a large registry of patients [53]. An observation analysis of 255,901 hospitalized with heart failure (of whom 117,761 had reduced ejection fraction) from 398 hospitals participating in the Get with the Guidelines-HF registry between 2005 and 2014, only 19.7 % of patients received digoxin at discharge. The frequency of digoxin prescription in all patients with reduced ejection fraction has decreased from 33.1 % in 2005 to 10.7 % in 2014. Patient factors associated with digoxin use include atrial fibrillation, presence of ICD, chronic obstructive pulmonary disease, diabetes mellitus, younger age, and lack of renal insufficiency (Table 1).

Conclusion/Discussion

The role of digoxin in patients with systolic dysfunction remains to be fully elucidated. Given that no contemporary randomized clinical trials have been performed using digoxin, we cannot make any definitive statements regarding efficacy in the modern era. The many observational studies as well as retrospective and post-hoc analysis are fraught with bias, even when sophisticated statistical methods have been used to attempt to eliminate such bias. As far as looking at digoxin use in clinical practice, this may be more of a marker of heart failure severity rather than the cause of increased mortality in the heart failure population. It should be noted that digoxin has inotropic properties, and all other inotropes presently used for heart failure are associated with an increased mortality risk, largely due to worsening arrhythmias. In comparison to other inotropic agents, digoxin has not been consistently linked to increased mortality, and in many studies has proven to be effect neutral or beneficial on mortality which may be due to the fact that it does not increase heart rate while also decreasing sympathetic tone. Furthermore, as we have identified a narrower therapeutic window than what was originally used in the early trials of digoxin, few studies have bolstered the mortality benefit of digoxin within a narrower concentration of <1.0 ng/mL. What remains important and at times overlooked is that in the largest randomized trial to date, the DIG trial, digoxin was shown to reduce heart failure admissions, which is an important and scrutinized metric which can decrease the economic burden imposed by this disease. Finally, an improvement in heart failure symptoms and quality of life is not insignificant as what patients tend to care about most is feeling better.

What is needed are randomized controlled trials using digoxin in the modern era of systolic heart failure therapy, including one for initiation in decompensated hospitalized patients looking at 30-day readmission rates. Moreover, in an

Table 1 Summary of contemporary studies looking at the effects of digoxin use in patients with heart failure: All except the DIG trial are retrospective analyses or prospective cohort studies

Study	Year	Average LVEF%	Average Age	% on ACE/ARB	% on diuretic	% on Beta-blocker	Effect of Digoxin
DIG [2]	1997	28	64	94	81	Unknown	Reduction in hospitalization; Trend toward decreased mortality attributed to worsening HF
RALES [41]	1999	25	65	95	100	10	Mortality benefit of spironolactone only seen in patients also taking digoxin
Val-HeFT [39, 40] Butler et al.	2001	27	63	92	85	35	Increased all cause mortality and HF hospitalizations
Domanski et al. [37] SOLVD trial analysis	2005	<35	60 (M) 62 (F)	49 (M) 48 (W)	71 (M) 82 (F)	8	No mortality differences in gender
Freeman et al. [42]	2006	–	69	45-47	35	50	New digoxin prescription associated with increased mortality in patients with heart failure with LVEF ≤40 %, no difference in HF hospitalizations
Dhaliwal et al. [38]	2008	23	68	80	93	63	No mortality or readmission benefit
Georgiopoulou et al. [44]	2009	18	52	73	100	45	No mortality or reduction of hospitalization in patients with advanced heart failure
Ahmed et al. [43]	2012	–	75	69	85	32	Lowered 30 day all cause hospital readmissions
Shah et al. [48]	2014	–	80	65.9	87.7	48	Associated with increased mortality in patients with atrial fibrillation and systolic heart failure, but less so than in patients with atrial fibrillation without heart failure

ideal world, it would be interesting to conduct a randomized trial with a less heterogeneous population of systolic heart failure than what was included in the Dig trial, in order to target higher risk ambulatory patients with lower EF, lower blood pressure, and more advanced heart failure. Although a trial like this is very unlikely to happen, one would surmise that this population may have a more significant benefit, as we have seen from post hoc analyses already described. One could ask the question: Would we expect a stable, chronic heart failure patient who is NYHA I or II with an LVEF of 40 % to benefit from the addition of digoxin? We would likely answer no, in contrast to a patient with an EF of 20 %, NYHA III symptoms of heart failure, and a lower systolic blood pressure. As an analogy, if we used cardiac resynchronization therapy (CRT) for all comers, how many more non-responders would we have? We know now that the criteria for applying CRT is narrower than we originally thought, and we have changed our guidelines to include only those with features that would favor a response. In our opinion, the DIG trial was an example of too wide of an inclusion criteria and does not reflect the actual purpose needed in the appropriate patients, noting that 67 % in each group were NYHA class I or II. What will be important moving forward is identifying subgroups who will most benefit from digoxin as well as applying safe dosing nomograms to minimize toxicity.

It is in the authors' experience, as it was shown to be the case in earlier studies in the 80s and 90s, that heart failure patients who derive the most benefit from digoxin are those with lower EF, more dilated ventricles, and lower blood pressure. Patients who are decompensated with low cardiac output (either clinically or confirmed by right heart catheterization), with a resting tachycardia, and especially those with an S3 gallop, are particularly benefited by the addition of digoxin, which leads to a reduction in heart rate, improvement in renal function and urine output, and an increase in blood pressure allowing tolerance to vasodilators and ultimately beta blockers. At our institution, an approach to decompensated hospitalized heart failure patients is to consider digoxin initiation along with other simultaneous measures including diuretics and, in appropriate patients, vasodilators. The several hundred year history of digoxin, its known hemodynamic and neurohormonal benefits, the primary findings of the DIG trial, and the wealth of clinical experience gained by practicing clinicians in cardiology, should not be erased or marginalized by subsequent epi-based, observational, and retrospective analyses that do not give insight into how the drug is being used. Although many questions remain to be answered, despite its controversial history, digoxin remains a viable therapeutic option in the management of heart failure symptoms and reduction in hospitalizations even among the current armamentarium of heart failure therapies.

Compliance with Ethical Standards

Conflict of Interest Chonyang L. Albert, Forum Kamdar, and Mazen Hanna declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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