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Is Digoxin a Risk Factor or a Risk Marker in Heart Failure with a Low Ejection Fraction?

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ABSTRACT

Digoxin is a compound that has been utilised in cardiovascular therapy for a long time. Nonetheless, its mode of action and, more crucially, its clinical value have been a source of contention. Digoxin has positive inotropic and neurohormonal modulation effects, and it has been the mainstay of heart failure therapies for decades. Digoxin prescription rates have been in free decrease since the introduction of β-blockers and aldosterone antagonists as part of modern heart failure medical care. The fact that digoxin is still recommended as a treatment option in both American and European heart failure guidelines hasn't changed specialists' minds.A succession of papers based primarily on observational studies and post hoc analysis has raised questions about the clinical efficacy and long-term safety of digoxin since the release of the initial Digitalis Investigation Group trial findings. We will conduct a thorough assessment of the available clinical evidence on the efficacy and safety of digoxin in heart failure patients with a lower ejection fraction in this paper. Individual studies' methodological challenges, strengths, and limitations will be emphasised.

Keywords: Digoxin,Heart failure,Reduced ejection fraction

INTRODUCTION

Digoxin is a pure cardiac glycoside derived from the foxglove plant that has been in therapeutic use since William Withering first described it in 1785. For decades, digoxin was the gold standard in heart failure (HF) treatment, until a paradigm shift in HF pathophysiology led to a move from inotropic support to neurohormonal modulation. Despite being widely approved by both the American College of Cardiology Foundation/American Heart Association [1] and the European Society of Cardiology [2] HF guidelines, with IIa and IIb class recommendations, digoxin use is steadily decreasing [3].At least two factors could explain why clinicians are hesitant to prescribe digoxin: first, there is much uncertainty about its clinical efficacy in modern HF patients, and second, a series of reports on increased risks associated with long-term digoxin use, presumably due to its proarrhythmic properties, have cast doubt on its safety. We will examine the existing evidence on the use of digoxin in the treatment of HF patients with a decreased ejection fraction(EF) in this narrative review.

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DIGOXIN: MECHANISM OF ACTION AND TOXICITY

Digoxin binds to the sarcolemmal Na^+-K^+ ATPase pump, preventing Na+ from being extruded outside of the myocyte in exchange for K^+. As the Na^+-Ca^{++} exchanger promotes Ca^{++} influx over outflow, gradually increasing Na^+ ions inside the sarcoplasma leads to a subsequent increase in internal Ca^{++} concentration. During diastole, calcium is transferred to the sarcoplasmic reticulum, where it is stored. A bigger amount of Ca^{++} is released when the next depolarizing im- pulse reaches the myocyte, resulting in a more powerful contraction during excitation-contraction coupling [4].Furthermore, evidence from experimental research supports the hypothesis that cardiac glycosides affect cardiac ryanodine receptor-2 directly [5]. Digoxin has negative chronotropic properties in addition to its favourable inotropic effects; increasing intracellular Ca^{++} levels lengthen phase IV and phase 0 of the cardiac action potential, lowering the heart rate.

However, the same mechanism that explains digoxin's activity is most likely also responsible for its toxicity. Progressively increasing Ca^{++} ions eventually exceeded the sarcoplasmic reticulum's storage capacity, triggering the forward mode of the Na^+-Ca^{++} exchanger and a transitory inward depolarizing current. This is thought to be the electrophysiological mechanism that causes delayed after-depolarizations, which can lead to polymorphic ventricular tachycardia as a result of triggered activity [4, 6].

DIGOXIN: ORAL INOTROPE AND NEUROHORMONAL MODULATOR

Digoxin has been shown to improve hemodynamic effects by improving EF and cardiac index [7, 8], as well as lowering pulmonary capillary wedge pressure [9]. In patients with severe HF and increased left ventricular filling pressures, intravenous digoxin treatment has been shown to minimise cardiac norepinephrine spillover [10]. Oral digoxin medication resulted in a considerable decrease in plasma norepinephrine levels in patients with chronic HF [11, 12]. Intriguingly, digitalis glycosides appear to have a different physiologic effect on HF patients than on healthy people.In HF patients, intravenous dioxin boluses resulted in a decrease in forearm vascular resistance and a prolonged decrease in efferent sympathetic nerve activity to the muscles, but not in healthy people. Dobutamine had no effect on the above two in- dices despite a comparable increase in cardiac index [13], indicating that this sympathoinhibitory response to digoxin is unrelated to its positive inotropic activity. Digoxin may improve carotid sinus baroreflex sensitivity [12] by limiting acute resetting of baroreceptors, lowering sympathetic nervous system activity indirectly [14, 15].Apart from its sympatholytic effects, digoxin raises cardiac vagal tone, which results in a rise in heart rate variability [8, 11, 12]. During sinus rhythm, digoxin lowered heart rate by an average of 4–7 beats per minute [16–18]. Finally, digoxin therapy has been connected to a rise in plasma brain natriuretic peptide levels [20], whilst digoxin discontinuation has been linked to a drop in plasma renin activity [19]. It's worth noting that the drug's favourable neurohormonal effects are visible even at low maintenance doses [7, 8], and that subsequent dose escalation may provide some additional inotropic support but no further decrease in neuroendocrine activation [7].

EARLY RANDOMIZED CLINICAL TRIAL DATA

PROVED is a randomised, double-blind, that enrolled 88 individuals with chronic HF with sinus rhythm who had mild to moderate symptoms. At the start of the trial, all of the subjects were taking diuretics and digoxin. The patients were given the option of having their digoxin or continuing to take their digoxin. Patients who stopped taking digoxin had a worsening of their maximal exercise capacity, as well as a higher rate of treatment failures. Patients in the active therapy group, on the other hand, maintained a lower body weight and heart rate, as well as a greater EF [21].

The Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) study comprised 178 chronic HF patients with New York Heart Association (NYHA) class II or III symptoms, EF 35 percent, and sinus rhythm in a randomised, double-blind. Diuretics, digoxin, and angiotensin-converting enzyme inhibitors were all part of the initial treatment plan (ACEi). Patients were assigned to continue receiving digoxin. Patients who were taken off digoxin had a worsening of their HF status as well as a deterioration of their general functional ability, as evidenced by a decrease in their maximal exercise tolerance and a worsening of their NYHA class. Patients who continued to take digoxin had a higher EF, as well as a decreased weight and heart rate.[16].

Uninterrupted digoxin medication was effective regardless of baseline serum digoxin concentrations in a pooled analysis of the two studies mentioned above (SDC). Patients in the lower-SDC group were less likely to have worsening HF symptoms and maintained a greater exercise capacity, while their EF did not deteriorate [22].

The Dutch Ibopamine Multicenter Trial (DIMT) recruited 59 chronic HF patients with a mean EF of 30% and mild to moderate symptoms who were treated only with diuretics in a randomised. Patients were randomly assigned to receive ibopamine, or digoxin in a 1:1:1 ratio. When compared to digoxin therapy, but not ibopamine, was linked with a significant increase in activity time at 6 months [19].

THE DIGITALIS INVESTIGATION GROUP STUDY

These promising early results prepared the door for a bigger investigation, the Digitalis Investigation Group (DIG) study [23]. This was a randomised, double-blind involving 6,800 chronic HF patients, most of whom were NYHA class II-III and had an EF of less than 45 percent. The participants were randomly assigned to receive digoxin with all-cause death as the primary goal. It's worth noting that >94% of patients were taking an ACE inhibitor and >80% were using a diuretic. There was no difference in all-cause mortality between the two research groups after 37 months of follow-up.Digoxin-treated patients were 6 percent less likely to be admitted to the hospital. Digoxin was linked to relative risk reductions of 13 and 28 percent in hospitalisation rates for cardiovascular reasons and worsening HF, respectively. Furthermore, while there was a clear tendency toward lower mortality owing to worsening HF in the digoxin arm ($p = 0.06$), there was also a higher death rate ($p = 0.04$) due to other cardiac causes – likely arrhythmias – despite the latter not being a pre-specified goal.

POST HOC ANALYSES OF DIG DATA

Rathore et al. [24] found a 5.8% absolute increase in the all-cause death rate among female patients assigned to digoxin compared to their male counterparts in a post hoc analysis of DIG trial data, indicating a substantial treatment-gender interaction. Following that, the same group of authors concentrated on male patients who were alive one month after randomization and had SDC measurements available. When compared to men those with SDC in the lower range (0.5–0.8 ng/ml) exhibited a 20% relative risk reduction in all-cause mortality and a 44 percent relative risk reduction in HF hospitalisation rates. Patients with SDC in the top range, i.e., 1.2 ng/ml, on the other hand, had an 11.8 percent absolute increase in all-cause mortality [25].

These two findings triggered a discussion about a putative digoxin-gender connection and prompted a review of the standard SDC treatment range. However, additional post-hoc analysis of the DIG [26, 27] and Studies of Left Ventricular Dysfunction (SOLVD) data [28] failed to reproduce Rathore et al [24] results of an increased risk in women. In a reanalysis of the SOLVD data, Domanski et al. [28] found no evidence that women treated with digoxin had higher all-cause or cause-specific mortality than their male counterparts. Data on SDC, on the other hand, was not collected.Adams et al. [26] focused on a subset of DIG patients ($n = 4,944$) of both genders who were alive one month after randomization and had SDC measurements

available. Women with SDC in the lower range, i.e. 0.5–0.9 ng/ml, had death rates and a significant 30% reduction in HF-related hospital admissions. However, among women with SDC levels ranging from 1.2 to 2.0 ng/ml, there was a marginal statistically significant increase in all-cause death.Men showed a similar trend, with a substantial reduction in both mortality and morbidity endpoints at low SDC, but all mortality benefits were muted at increasing SDC, though the finding of reduced hospital admissions continued [26].

Finally, Ahmed et al. [29] evaluated the data of the full DIG population – including those participating in the auxiliary study – who were still alive at 1 month post-randomization and had SDC determined (n = 5,548), regardless of sex or initial EF. Patients with an SDC of 0.5–0.9 ng/ml showed a relative risk reduction in all-cause mortality and HF hospitalizations of 23 and 38 percent, respectively, during a median follow-up period of 40 months. Patients with an SDC of less than 1 ng/ml, on the other hand, had mortality rates identical, despite a significant 32 percent relative risk decrease in HF hospitalizations [27].

DIGOXIN IN CONTEMPORARY HF PATIENTS

Following the publication of the DIG trial, a series of reports on the impact of digoxin on clinical outcomes in patients with congestive heart failure (HF) who were taking ACEi/ angiotensin-converting enzyme inhibitors (ACEI), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin-converting enzyme inhibitors (ACEI). Dhaliwal et al. [30] investigated the effect of digoxin on all-cause mortality and/or HF readmissions in 347 patients discharged with a diagnosis of systolic HF in an observational trial. These individuals were on a combination ofβ-blockers and ACEi/ARBs as a back-up treatment. Digoxin medication was not associatedwith a decreased rate of all-cause mortality or fewer HF-related hospital admissions after adjusting for a number of possibly confounding variables [30].

In a retrospective analysis involving 455 patients who were referred for transplant evaluation, the efficacy and safety of digoxin were once again questioned. It should be highlighted that more than 90% of the patients were using ACE inhibitors, angiotensin converting enzyme inhibitors, and β-blockers, half were taking aldosterone antagonists and digoxin, and 60% had an implantable cardiac defibrillator. More than twice as many digoxin-treated patients met the composite endpoint of death, urgent transplantation, or ventricular assist device implantation after a median follow-up time of 27 months compared to those who did not take the medicine. There was no difference in the rates of all-cause or HF-related hospital admissions between the two groups [31].The findings of a retrospective study of Valsartan in Heart Failure Trial (Val-HeFT) data were published in the same vein [32]. A total of 5,010 symptomatic HF patients were enrolled in the initial Val-HeFT research, with 3,374 (67%) of those taking digoxin at the start. Digoxin medication was linked to a greater risk of all-cause mortality and HF-related hospitalizations after adjusting for baseline differences between groups [32].

In a large (n = 2,891) cohort of patients with newly diagnosed systolic HF, the effect of digoxin on all-cause mortality and HF hospitalizations was recently studied. About half of the patients were on ACEi/ARBs and a similar amount were on β-blockers at the start of the study, while nearly 20% were given digoxin for the first time (incident digoxin users). After multivariate correction for baseline between-group differences, patients treated with digoxin had a 72 percent increased relative risk of death compared to non-digoxin users after a median follow-up of 2.5 years. Furthermore, there was no difference in HF hospitalisation rates [33].

In 350 patients with ischemic heart disease who received a cardiac resynchronization therapy defibrillator for primary prevention according to current guidelines, Adelstein et al. [34] investigated the influence of digoxin on suitable implantable cardioverter defibrillator therapies. 46 percent of research patients were put on digoxin after implantation, and the average follow-up period was 48 months. There was a substantial difference in the time to the first appropriate shock among digoxin-treated patients, but there was no difference in the rates

of appropriate antitachycardia pacing therapy. The proarrhythmic effect of digoxin was more prominent in patients with an EF of less than 22%.

A post hoc study of data from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) backed with the previous findings. Digoxin was used by 26% of the patients at the start of the study. Between digoxin users and nonusers, the 4-year cumulative risk of death was not statistically different. The same was true for heart failure hospitalisation rates and the combined endpoint of mortality or heart failure-related hospitalisation. Digoxin use, on the other hand, was linked to a significant 41 percent increase in the relative risk of ventricular tachycardia/fibrillation, mostly due to a 65 percent increase in the relative risk of high-rate episodes 200 beats/min [35].

META-ANALYSES EVALUATING THE ROLE OF DIGOXIN

Vamos et al. [36] identified 19 publications on the effect of digoxin on all-cause mortality in individuals with atrial fibrillation, heart failure, or both. Digoxin use was linked to a slight, but substantial, 14 percent increase in the relative risk of all-cause death in nine trials involving solely HF patients (n = 91,379) [36]. The opposite conclusion was reached by Ziff et al. [37] in another meta-analysis. A total of 52 studies were examined, with data from 621,845 patients pooled together. In unadjusted and adjusted studies, as well as in propensity-matched cohorts, the death risk ratio was higher for digoxin users, while it was neutral in randomised controlled trials.There was no difference in all-cause mortality between those randomised to digoxin when data from seven randomised controlled trials with a total of 8,406 individuals was analysed. Furthermore, regardless of the research design, digoxin reduced all-cause hospital admissions by 8%, which is a small but significant reduction.

DISCUSSION

CRITICISM OF PROVED AND RADIANCE

Patients with ambulatory HF who were stable on chronic digoxin therapy were randomised to continue on digoxin in the PROVED [21] and RADIANCE [16] studies. Withdrawal studies, on the other hand, are unable to provide a definitive answer as to whether a specific treatment was required in the first place. Furthermore, the efficacy of the medicine under examination is frequently overestimated in trials of a comparable type. Patients who were stable on digoxin before entering the research are more likely to worsen once the medicine is removed. Finally, just a small number of patients were enrolled in both investigations, there was a short follow-up period, and no hard goals were measured.

SCRUTINIZING THE DIG TRIAL

The DIG [23] experiment was a major, multicenter, randomised, double-blind in which 6,800 chronic HF patients were randomly assigned to digoxin. The median follow-up time was more than three years, and the major endpoint was all-cause death, which was the most difficult to measure. Overall, three parts of the DIG experiment have received the greatest attention: patient enrollment, background medical therapy, and digoxin dose.

Looking at the DIG population baseline data, it's obvious that 44.1 percent of digoxin patients were already on digoxin prior to study admission, whereas 44.6 percent patients were already on stable, chronic digoxin medication. It's worth noting that none of these patients had completed a washout period prior to enrolling in the trial. As a result, around a quarter of the DIG participants were in a digoxin withdrawal trial, while another quarter were evaluated for prevalent rather than incident digoxin medication. Opie [38] raised serious doubts in an interesting editorial about whether the DIG research would have yielded the same results if digoxin had been given on top of ACEi and diuretics in really digoxin-naive patients [38].

The second fundamental flaw, which limits the relevance and generalizability of the DIG trial results in current HF patients, is the study participants' background therapy. The DIG study took place in the early 1990s, when β-blockers and aldosterone antagonists were not often utilised in HF patients, and device-based therapy was also not a possibility.In an attempt to defend digoxin and the relevance of the DIG results, Gheorghiade et al. [39] pointed out that -blocker studies [40–42] were done on populations with substantial background usage of digoxin, and that one may argue that β-blockers are useless in the absence of digoxin. In a similar vein, early clinical trials establishing the function of ACEi in HF were undertaken before the advent of betaβ-blockers [43, 44], but ACEi are still regarded the cornerstone of HF therapy.

Finally, a final flaw in the DIG experiment is the dose of digoxin. Since SDC values up to 2 ng/ml were considered therapeutic around the time the study was conducted, the median daily digoxin dose was 250 μg. However, it was later discovered that SDC levels more than 1 ng/ml were linked to poorer results, and the ideal SDC range was reduced to 0.5–0.9 ng/ml [27]. Maintaining SDC within such a limited range in real-life patients can be difficult, to say the least.Patients with advanced HF are typically elderly, have impaired renal function and other comorbidities, and are taking multiple drugs that may either directly impair kidney function (e.g., ACEi/ ARB) or indirectly elevate digoxin levels due to drug-drug interactions (e.g. via P-glycoprotein inhibition). A daily digoxin dose of ≤125μg was found to be the strongest independent predictor of a low SDC (e.g. 0.5–0.9 ng/ml) in a subgroup of the DIG experiment [45].

Experimental evidence supports the argument that cardiac glycosides can block the fast component of a delayed potassium rectifier current even at nanomolar values, adding another degree of complexity to the optimal-SDC issue [46]. This could cause action potential lengthening, predisposing cardiac myocytes to electrical instability through a mechanism similar to that of class III Vaughan-Williams antiarrhythmic medicines. Furthermore, digoxin is distributed not only in plasma but also in the peripheral nonserum compartment; it has also been argued that digoxin's clinical effects and toxicity are unrelated to its plasma levels, and therefore customising the digoxin dose based on the SDC could be misleading [47].

Regrettably, there are no clinical research explicitly designed to evaluate the notion of whether reduced SDC actually translates into a lower arrhythmic risk. Contemporary HF medications, like as β-blockers and spironolactone, which both help to maintain proper potassium levels, should theoretically help to reduce digoxin-related proarrhythmia. The results of a prespecified subgroup analysis in the Randomized Aldactone Evaluation Study (RALES), which found that spironolactone reduced all-cause mortality among those on background digoxin medication, corroborate the latter approach [48]. It's worth noting that more than 70% of patients in both arms of the RALES were taking digoxin.

POST HOC ANALYSES

Post hoc evaluations of randomised clinical trial data [32, 35] have a common feature in common with observational studies: digoxin treatment is not randomised. As a result, the idea that digoxin should have been reserved for sicker patients with a poorer prognosis seems plausible. Patients on digoxin were more symptomatic, had lower EF and blood pressure, and were less likely to be on concomitant -blocker therapy, according to the Val- HeFT post hoc study [32].The same may be said for the MADIT-CRT post hoc analysis, in which residual confounding could not be ruled out after substantial correction for baseline between-group differences, according to the authors [35]. Prescription bias against digoxin appears to be widespread, according to Ziff et al. [37]. The fact that digoxin is currently regarded a second-line treatment for both HF and atrial fibrillation indications is an obvious explanation; thus, this medicine is reserved for patients who have already failed first-line treatments.

PROPENSITY SCORE MATCHING

Propensity score matching is a technique for reducing bias in the evaluation of treatment outcomes by taking into account the factors that predict treatment acceptance in the first place. It's an attempt to approximate randomization by matching two groups of people based on a variety of criteria to make them more comparable. The fact that only differences in the measured covariates may be balanced is an obvious disadvantage of this strategy. Cleland and Cullington [49] emphasised the possible problems of propensity matching in a state-of-the-art editorial, particularly when used to assess the effect of a medicine that improves a range of parameters that, on their own, suggest a better prognosis.According to Cleland and Cullington [49], a patient whose EF improves after receiving digoxin will be matched to a patient with a similar EF who does not receive digoxin; if both patients have an uneventful course during follow-up, the beneficial effect of digoxin will be masked by the improvement in EF. Furthermore, propensity matching requires large samples and a sufficient overlap between the treatment and control groups; otherwise, the danger of matching the worst cases in the treatment group to those in the control group with the best set of features or vice versa is high.

META-ANALYSES

Meta-analysis is, without a doubt, the most reliable analytical tool for extracting high-quality information, which is designated as level-of-evidence A in guidelines documents. The quality of the raw data given by each individual study, however, has a significant impact on the reliability and robustness of meta-analysis conclusions. Patients on digoxin were sicker and used more diuretics in the 52 trials that Ziff et al. [37] included in their meta-analysis, implying more severe HF.Meta-regression analyses revealed that baseline differences between study groups could have a significant impact on the observed mortality rates attributed to digoxin and that the better the study design (randomised controlled trials vs. observational studies), the less likely it was to report a difference in survival rates between digoxin and non-digoxin users [37].

Despite considerable breakthroughs in HF therapy and the establishment of national standards and penalties enforcing strict adherence to recommendations, 30-day hospital readmission rates remain at a shocking 20% [52]. According to Vaduganathan et al. [53], this increased early risk of readmission is more likely owing to hemodynamic abnormalities than to true disease progression. Digoxin raises the EF and cardiac output while lowering the pulmonary capillary wedge pressure [7–9], which reflects its mechanism of action.Digoxin slows heart rate and has no effect on blood pressure, therefore it can be safely given to patients with borderline blood pressure, unlike β-blockers and ACEi/ARB. Furthermore, digoxin was associated with an improvement in renal function in a subset of DIG patients [54], defined as an increase of more than 20% in estimated glomerular filtration rate; thus, unlike renin-angiotensin-aldosterone system inhibitors, it can be used in patients with marginal kidney function without the risk of further renal impairment.

In this regard, digoxin may play a significant role when administered as an adjuvant medication on top of disease-modifying, life-prolonging HF therapy with the goal of reducing hospitalizations.Digoxin treatment was associated with a 44 percent relative risk reduction in 30-day all-cause and HF-related hospitalisation rates in a subset of 3,405 DIG patients aged 65 years or older with a decreased EF [55]. However, these findings should be viewed with caution because this significant effect was more prominent in a subset of individuals who were on chronic digoxin therapy and hence more prone to worsen when the drug was stopped.

PATIENTS MOST LIKELY TO RESPOND FAVORABLY TO DIGOXIN

Female gender, hypertension, and a relatively preserved EF were among the clinical characteristics of patients who seemed to derive less benefit or even harm from digoxin therapy, which meant no decrease in HF-related admissions or an increase in all-cause mortality, according to a cluster analysis of original DIG population data. Patients with congestion, S3 gallop, lower systolic blood pressure, and more severe systolic dysfunction, on the other hand, had fewer hospital admissions and no increased mortality [56].In a similar vein, digoxin treatment was associated with a lower in- incidence of the combined endpoints of HF-related mortality/hospitalization and all-cause death/hospitalization at 2 years in the three DIG protocol-prespecified high-risk groups, i.e., NYHA class III–IV symptoms and cardiothoracic ratio >55 percent or EF 25 percent [39].

CONCLUSIONS

In summary, the clinician must choose between high-quality data derived from clinical trials conducted more than two decades ago, before modern HF therapy was available, and less-strong evidence derived primarily from observational studies and post-hoc analyses, albeit including current HF populations. Realistically, given the lack of corporate support, another clinical trial of the scale of the DIG is unlikely to be funded. Nonetheless, cardiac glycosides should not be ruled out of the HF arsenal, in our opinion.Patients with severe HF and symptoms of congestion who are unable to tolerate high dosages of disease-modifying medications because to borderline blood pressure/renal function are likely to benefit from digoxin. To reduce the risk of toxicity, digoxin should be administered to reduce hospital readmissions, while SDC, creatinine, and potassium levels should be regularly monitored.

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