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Digoxin as a Treatment Option for Heart Failure with Reduced Ejection Fraction

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***Abstract*: Digoxin is a cardiovascular drug obtained from the plant leaf of Digitalis lanata. Digoxin has a long history of usage in cardiovascular treatment. There is ongoing discussion over this drug's mode of action and therapeutic effectiveness. Positive inotropic and neurohormonal modulation effects of digoxin are found. Since the advent of beta-blockers and aldosterone antagonists as components of modern heart failure therapy, the rate of digoxin prescriptions has fallen. American and European heart failure therapy recommendations still include digoxin as a possible course of action. Since the first Digitalis Investigation Group trial findings were made public, observational studies and post hoc analyses have raised concerns about the clinical efficacy and long-term safety of digoxin. In this review, we analyze the clinical evidence, effectiveness and the safety of digoxin in patients with heart failure and lower ejection fraction.**

***Keywords*: Digoxin, Heart Failure (HF), Ejection fraction (EF), Patients.**

1. Introduction

Since William Withering originally characterized digoxin in 1785, it has been a pure cardiac glycoside that is extracted from the leaf of the Balkan foxglove and Digitalis lanata plants. Digoxin served as the gold standard in the treatment of heart failure (HF) for many years, but a paradigm change in the pathophysiology of HF caused the focus to shift from inotropic support to neurohormonal modulation. Digoxin use is progressively declining despite being broadly endorsed by the American College of Cardiology Foundation, American Heart Association, and European Society of Cardiology HF guidelines, with IIa and IIb class recommendations [1]-[3]. There are two reasons why doctors might be reluctant to recommend digoxin:

i. There is a great deal of controversy regarding its therapeutic effectiveness in contemporary HF patients, and
ii. A number of papers have raised concerns about the safety of long-term digoxin usage due to elevated risks, likely brought on by its proarrhythmic qualities.

We will discuss the data that is currently available on the use of digoxin in the treatment of HF patients with a reduced ejection fraction in this review.

2. Digoxin: Mode of Action and Toxicity

Digoxin prevents Na^+ from leaving the myocyte in exchange for K^+ by binding to the sarcolemmal Na^+ - K^+ ATPase pump. The sarcoplasma progressively builds up Na^+ ions as a result of the Na^+ - Ca^{++} exchanger favouring Ca^{++} influx over outflux, which causes a subsequent increase in intracellular Ca^{++} concentration. Calcium is transported to and stored in the sarcoplasmic reticulum during diastole. When the subsequent depolarizing impulse reaches the myocyte, more Ca^{++} is released, which causes a stronger contraction during excitation contraction coupling [4]. Additionally, evidence from experimental studies backs up the idea that cardiac glycosides directly alter cardiac ryanodine receptor-2 [5]. In addition to its positive inotropic effects, digoxin also exhibits negative chronotropic properties that prolong phase IV and phase 0 of the cardiac action potential, slowing the heart rate. However, digoxin's toxicity is probably caused by the same process that gives rise to its action. Ca^{++} ions build up to the point that they can no longer fit in the sarcoplasmic reticulum, which activates the forward mode of the Na^+ - Ca^{++} exchanger and causes a brief inward depolarizing current. Due to triggered activity, delayed after depolarization is assumed to constitute the electrophysiological mechanism that generates polymorphic ventricular tachycardia [4], [6].

3. Role of Digoxin as Oral Inotrope and Neurohormonal Regulator

Digoxin has been demonstrated to enhance hemodynamics by increasing the ejection fraction (EF) and cardiac index as well as decreasing the pulmonary capillary wedge pressure [7]-[9]. Digoxin therapy administered intravenously has been demonstrated to reduce cardiac norepinephrine spillover in individuals with severe HF and elevated left ventricular filling pressures [10]. In those with chronic HF, oral digoxin therapy significantly reduced plasma norepinephrine levels [11], [12]. It is interesting to note that digitalis glycosides seem to affect physiology differently in HF patients compared to healthy

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individuals. Intravenous digoxin boluses reduced forearm vascular resistance and prolongedly decreased efferent sympathetic nerve activity to the muscles in HF patients, but not in healthy individuals. Despite a comparable increase in cardiac index, dobutamine had no effect on the aforementioned two indices [13], showing that the sympathoinhibitory response to digoxin is unrelated to its beneficial inotropic activity. By restricting acute baroreceptor resetting, digoxin may indirectly diminish sympathetic nervous system activity and increase carotid sinus baroreflex sensitivity [12], [15]. Digoxin increases cardiac vagal tone in addition to its sympatholytic actions, which increases heart rate variability [8], [11], [12]. Digoxin reduced heart rate by 4 to 7 beats per minute on average during sinus rhythm [16]-[18]. The levels of plasma brain natriuretic peptide have been shown to increase with digoxin therapy [20], whilst plasma renin activity has been shown to decrease upon digoxin withdrawal [19]. It is important to note that the drug's beneficial neurohormonal effects can be felt even at low maintenance doses [7], [8], and that subsequent dosage escalation may provide more inotropic support without further decreasing neuroendocrine activity [7].

4. Randomized Clinical Trial Data

In the PROVED study (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin), 88 patients with mild to severe chronic HF symptoms and sinus rhythm were included. All of the test individuals were taking digoxin and diuretics at the beginning of the experiment. The patients were offered the choice of continuing to take digoxin or having their digoxin replaced with a placebo. The maximal exercise capacity and the rate of treatment failure decreased in those who stopped taking digoxin. On the other hand, patients in the active treatment group, kept their body weight and heart rate lower while having higher EF [21].

In a randomised double-blind, placebo-controlled study, 178 chronic HF patients with New York Heart Association (NYHA) class II or III symptoms, EF<35%, and sinus rhythm participated in the Randomized Assessment of Digoxin on Inhibitors of Angiotensin Converting Enzyme (RADIANCE) study. Angiotensin converting enzyme inhibitors, digoxin, and diuretics were administered from the beginning of this treatment. Patients had the choice of continuing their digoxin treatment or switching to a placebo. Patients who were taken off digoxin had a greater rate of their HF deteriorating, as shown by a decline in their maximum exercise tolerance and a deterioration of their NYHA class, as well as a reduction in their total functional ability. The EF, weight, and heart rate were all higher in patients who continued to take digoxin [16].

An analysis of the two aforementioned trials revealed that uninterrupted digoxin therapy was beneficial independent of blood digoxin levels. Patients in the lower SDC group were less likely to experience worsening of their HF symptoms and maintained a superior exercise capacity while their EF remained stable as compared to those receiving a placebo [22].

In a randomised, placebo-controlled study, 59 chronic HF patients with mild to moderate symptoms and a mean EF of 30 % were included in the Dutch Ibopamine Multicenter Study (DIMT). In a 1:1:1 ratio, patients were randomly assigned to receive placebo, ibopamine, or digoxin. Digoxin treatment, but not ibopamine administration, was associated with substantially longer exercise duration after six months [19].

5. Digitalis Investigation Group Study

The encouraging preliminary findings paved the way for the Digitalis Inquiry Group (DIG) research, a larger investigation [23]. 6,800 chronic HF patients participated in this randomised, double-blind, placebo-controlled study; the majority of them belonged to NYHA classes II to III and had an EF of less than 45 %. Digoxin or a placebo was given to the patients at random, with all-cause death being the main result. It is significant to highlight that > 80 % of patients used a diuretic, and > 94 % of patients were using an ACE inhibitor. After 37 months of follow-up, there was no difference in all-cause mortality between the two research groups. Patients using digoxin had a 6 % lower chance of being admitted to the hospital. In comparison to placebo, digoxin was associated with relative risk reductions of 13 % to 28 % in hospitalisation rates for cardiovascular issues and worsening HF. Additionally, despite the fact that arrhythmias were not a deliberate goal, there was a greater death rate ($p = 0.04$) due to other cardiac reasons like these despite the fact that there was a clear tendency toward decreased mortality due to worsening HF in the digoxin group ($p = 0.06$).

6. Post hoc Analyses of Digitalis Investigation Group (DIG) Data

In a post hoc examination of the DIG trial data, Rathore et al. [24] discovered a 5.8 % increase in the all-cause mortality rate among female patients assigned to digoxin compared to their male counterparts, demonstrating a significant treatment gender interaction. The same group then focused on male patients who had measurements of serum digoxin concentration (SDC) and were still alive at one month following randomization. Men with SDC in the lower range, 0.5 - 0.8 ng/ml, had a relative risk reduction of 44 % for hospitalisation for HF and a 20 % reduction in overall mortality. On the other hand, patients with SDC in the highest range, which is 1.2 ng / ml, saw an 11.8 % increase in all-cause mortality, which was significantly higher than those receiving a placebo [25]. These two results sparked debate about a potential digoxin-gender interaction and led to a review of the SDC treatment window. Rathore et al.'s [24] findings of a higher risk in women were not supported by additional post hoc analysis of the DIG [26], [27] and Studies of Left Ventricular Dysfunction (SOLVD) data [28]. Domanski et al. [28] reanalyzed the SOLVD data and found no evidence that women using digoxin had greater all-cause or cause-specific mortality than males. But no data on SDC was obtained. Adams et al.'s study [26] concentrated on a subgroup of DIG patients (n = 4,944) who were alive at one month after randomization and had access to SDC measurements. Death rates for women with SDC in the lower range, 0.5 - 0.9 ng/ml, were equivalent to those of placebo, and they experienced a significant 30 % relative risk reduction in HF-related hospital

admissions. The all-cause mortality rate, slightly rise among women with SDC levels between 1.2 and 2.0 ng/ml, which were statistically significant. Men had a similar trend, with significant reductions in mortality and morbidity endpoints at low SDC, whereas all mortality advantages were diminished at increasing SDC; the finding of fewer hospital admissions persisted [26].

Finally, regardless of sex or initial EF, Ahmed et al. [29] assessed the data of the whole DIG population, including those taking part in the supplemental study who were still alive at 1 month after randomization and had SDC determined (n = 5,548). During a median follow-up of 40 months, patients with an SDC of 0.5 - 0.9 ng/ml had a relative risk reduction in all-cause mortality and HF hospitalizations of 23 – 38 % compared to that on placebo. On the other hand, despite a considerable 32 % relative risk reduction in HF hospitalizations, individuals with an SDC of less than 1 ng / ml had mortality rates equal to those of placebo patients [27].

7. Use of Digoxin in HF Patients

Numerous investigations on the effects of digoxin on clinical outcomes in individuals using beta-blockers and angiotensin receptor blockers (ARB) were published after the publication of the DIG research. In an observational study, Dhaliwal et al. [30] examined the impact of digoxin on all-cause mortality and HF readmissions in 347 patients who were discharged with a diagnosis of systolic HF. These patients had a background therapy of beta-blockers, ACEi, and ARB. After controlling for a variety of potentially confounding characteristics, digoxin treatment was not associated with a reduced risk of all-cause mortality or fewer hospital admissions attributable to HF [30].

The efficacy and safety of digoxin were once more questioned in a retrospective investigation including 455 individuals who were submitted for transplant evaluation. The fact that more than 90 % of the patients were taking ACEi, ARB, and beta-blockers, half were also taking digoxin, and 60 % had implanted cardiac defibrillators, should be emphasised. After a median follow-up of 27 months, more than twice as many patients receiving digoxin treatment as those receiving placebo met the composite endpoint of death, urgent transplantation, or ventricular assist device implantation. The rates of hospital admissions for any reason or those linked to HF were the same for the two groups [31].

In a similar vein, the results of a retrospective analysis of the Valsartan in Heart Failure Trial (Val-HeFT) data were released [32]. The original Val-HeFT study involved 5,010 symptomatic HF patients, in which 3,374 (67 %) were digoxin-dependent at baseline. After correcting for baseline between-group differences, digoxin treatment was associated with a higher risk of all-cause death and HF-related hospitalizations [32].

A recent study looked at the impact of digoxin on all-cause mortality and HF hospitalizations in a sizable (n = 2,891) group of individuals with newly diagnosed systolic heart failure. At the beginning of the research, around 50 % of the patients were taking ACEi, ARBs, and beta-blockers, and a similar percentage were receiving digoxin for the first time. Digoxin-treated patients had a 72 % higher relative risk of death compared to non-users after multivariate adjustment for baseline differences between groups, according to a median follow-up of 2.5 years. Additionally, there was no difference in the rates of HF hospitalisation [33].

Accordance to current recommendations, in 350 patients with ischemic heart disease who received a cardiac resynchronization treatment defibrillator for primary prevention. Adelstein et al. [34] looked at how digoxin affected the best implantable cardioverter defibrillator therapies. Digoxin was prescribed to 46 % of trial participants after implant, with an average follow-up time of 48 months. Among digoxin-treated patients, the time to the first appropriate shock varied significantly, but there was no variation in the rates of effective anti-tachycardia pacing treatment. Digoxin's proarrhythmic effects were more pronounced in individuals whose EF was under 22 %.

The earlier findings were supported by a post hoc analysis from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). At the beginning of the research, 26 % of the patients were taking digoxin. The four-year cumulative risk of death was not significantly different between digoxin users and nonusers. The same was true for hospitalization rates for heart failure and the combined outcome of death or hospitalization for heart failure. Digoxin use was associated with a significant 65 % increase in the relative risk of high-rate episodes 200 beats per minute, which contributed to a major 41 % increase in the relative risk of ventricular tachycardia [35].

8. Meta-Analyses Evaluating the Role of Digoxin

19 articles investigating the effect of digoxin on all-cause mortality in people with atrial fibrillation, heart failure, or both were discovered by Vamos et al. [36]. In nine studies with just HF patients (n = 91,379), digoxin administration was associated with a small but significant 14 % increase in the relative risk of all-cause mortality [36]. Ziff et al. [37] discovered the opposite result in another meta-analysis study. A total of 52 studies were analysed, and 621,845 patient's data were combined. The mortality risk ratio was greater for digoxin users in unadjusted and adjusted studies, as well as in propensity-matched cohorts, although it was neutral in randomised controlled trials. When data from seven randomised controlled trials with a combined total of 8,406 participants were analysed, there was no difference in all-cause mortality between those randomised to digoxin and those on placebo. Digoxin also decreased hospital admissions by 8 %, which is a minor but significant reduction, independent of the trial type.

9. Discussion

A. Criticism of PROVED and RADIANCE

In the PROVED [21] and RADIANCE [16] investigations, patients with ambulatory HF who were stable on chronic digoxin treatment were randomised to stay on digoxin or move to a placebo. Withdrawal studies cannot provide a conclusive conclusion as to whether a certain therapy was initially necessary. Furthermore, in studies of the same kind, the

effectiveness of the drug under investigation is usually overstated. Before participating in the study, digoxin-stable patients are more likely to go worse when the medication is stopped. Finally, there were few patients in both investigations, there was little time for follow-up, and no end objectives were assessed.

B. Scrutinizing the DIG Trial

In the DIG [23] trial, 6,800 patients with chronic heart failure were randomly randomised to given digoxin or a placebo in a large, multicenter, randomised, double-blind, placebo-controlled study. The key endpoint was all-cause mortality, which was the most challenging to quantify, and the median follow-up period was more than three years. In general, patient recruitment, background medical treatment, and digoxin dose have drawn the most interest in the DIG project.

When comparing baseline data for the DIG population, it is clear that 44.1 % of digoxin patients were already taking the drug when they were admitted to the study, whereas 44.6 % of placebo patients were already on a steady, chronic dose of digoxin. It's important to note that none of these participants had finished a washout period before signing up for the experiment. As a result, around a quarter of the DIG participants were taking part in a digoxin withdrawal study, and a further quarter had their digoxin drug usage assessed as opposed to incidentally. In an intriguing commentary, Opie [38] challenges whether the DIG research would have produced the same results if digoxin had been given to digoxin-naive patients in addition to ACE inhibitors and diuretics [38].

The background therapy of the research participants is the second basic problem that restricts the applicability and generalizability of the DIG trial outcomes in contemporary HF patients. At the time of the DIG trial, beta-blockers and aldosterone antagonists were not often used in HF patients, and device-based therapy was also not an option. Gheorghiade et al. [39] argued that beta-blocker studies [40]-[42] were conducted on populations with high background digoxin usage and that one could contend that beta-blockers are ineffective in the absence of digoxin. This was done in an effort to defend digoxin and the relevance of the DIG results. Similar to this, early clinical studies confirming the role of ACEi in HF were conducted before beta-blockers were created [43], [44], although ACEi are still recognised as the cornerstone of HF therapy. The dose of digoxin is related to the DIG experiment. The median daily digoxin dose was 250 g since SDC levels up to 2 ng/ml were deemed therapeutic over the course of the research. Later research revealed that SDC concentrations over 1 ng/ml were associated with inferior outcomes, and the recommended SDC range was lowered to 0.5 – 0.9 ng/ml [27]. It can be challenging to keep SDC within such a narrow range in actual patients. Patients with advanced heart failure (HF) tend to be older, have impaired renal function and other comorbidities, and use several medications, some of which may directly impair kidney function (such as ACEi or ARB) or indirectly raise digoxin levels due to drug-drug interactions (e.g., via P-glycoprotein inhibition). The greatest independent predictor of a low SDC (e.g., 0.5 – 0.9 ng/ml) in a subset of the DIG experiment was found to be a daily digoxin intake of ≤ 125g [45].

This claim that cardiac glycosides can block the rapid component of a delayed potassium rectifier current even at nanomolar concentrations is supported by experimental evidence, which complicates the optimum SDC problem further [46]. As a result, cardiac myocytes may be more susceptible to electrical instability by a mechanism akin to that of class III Vaughan Williams antiarrhythmic medications. Digoxin is also distributed in the peripheral nonserum compartment in addition to the plasma, and it has been suggested that digoxin's clinical effects and toxicity are independent to its plasma levels, making it possible that tailoring the digoxin dose based on the SDC might be misleading [47].

There is no clinical research specifically designed to assess if a lower SDC really does translate into a lower arrhythmic risk. Theoretically, modern HF drugs like beta-blockers and spironolactone, which both support healthy potassium levels, should aid to lessen proarrhythmia caused by digoxin. The second strategy is supported by the results of a predefined subgroup analysis in the Randomized Aldactone Evaluation Study (RALES), which showed that spironolactone improved all-cause mortality relative to placebo only in those who were already taking baseline digoxin medication [48]. It's important to note that more than 70 % of RALES patients were also taking digoxin.

C. Observational Studies and post hoc Analyses

1) Observational Studies

The observational studies previously mentioned [30], [31], [33], [34] have an inherent weakness in that the treatment assignment is not the result of any randomised approach. Despite statistical adjustments, residual confounding caused by unmeasured factors cannot be completely eliminated. According to Dhaliwal et al. [30], there is a possibility of confounding by indication because patients who were discharged on digoxin had more severe left ventricular systolic dysfunction, a higher prevalence of atrial fibrillation, and more prior admissions due to worsening HF. They were also less likely to be hypertensive. The Kaiser Permanente Northern California database revealed a sizable, varied, community-based patient sample with newly diagnosed HF [33]. Without having to compare findings to the present medicine, the impact of incident digoxin use was examined. Additionally, the use of digoxin was thought to be a time-dependent variable, thus a result could only be linked to digoxin if the patient was taking it at the time of the incident. However, data on the traits and outcomes of the patients were acquired after the fact. Additionally, as with any observational study, there is always the chance of focusing on treatment results rather than a problem that is more pertinent to clinical practice, such assessing a therapy's response [33].

2) Post hoc Analyses

In observational studies, the digoxin therapy is not randomized, which is a typical feature of post hoc assessments of randomized clinical trial data [32], [35]. Therefore, it makes sense that digoxin should have been saved for sicker individuals

with a worse outlook. The Val-HeFT post hoc research [32] found that patients on digoxin were more symptomatic, had lower EF and blood pressure, and were less likely to be taking beta-blockers concurrently. The same is true for the MADIT-CRT post hoc analysis, where residual confounding could not be eliminated despite significant baseline between group differences being corrected [35]. According to Ziff et al. [37], there appears to be a sizable prejudice against digoxin in prescriptions. Digoxin is only prescribed to individuals who have already tried first-line therapy since it is now thought of as a second-line treatment for both HF and atrial fibrillation reasons.

3) Propensity Score Matching

By accounting for the variables that initially predict treatment acceptance, propensity score matching is a method for minimising bias in the assessment of treatment results. It is an effort to make two groups of individuals more similar by matching them based on a range of characteristics. This technique clearly has a drawback in that only variations in the measured variables may be balanced. The potential issues with propensity matching were highlighted by Cleland and Cullington [49] when it came to evaluating the effectiveness of a medication that improves a number of features that, on their own, indicate a better prognosis. According to the Cleland and Cullington study [49], if both patients have an uneventful course during follow-up, the beneficial effect of digoxin will be obscured by the improvement in EF for a patient whose EF improves after digoxin treatment when compared to a patient with a similar EF without digoxin. Additionally, propensity matching necessitates large samples and a high degree of overlap between the treatment and control groups. Without these conditions, there is a risk of matching members of the treatment group in the worst cases to those in the control group who have the best combination of features, or vice versa.

4) Meta-Analyses

Meta-analysis is categorized as level-of-evidence A in guideline publications and is without a doubt the most effective analytical strategy for obtaining high quality data. However, the reliability and robustness of meta-analysis results are significantly influenced by the quality of the raw data provided by each individual study. In the 52 studies that Ziff et al. [37] included in their meta-analysis, patients on digoxin were sicker and took more diuretics, suggesting more severe HF. Digoxin related mortality rates could be significantly impacted by baseline differences between study groups, according to meta-regression analyses. Additionally, the better the study design (i.e., randomised controlled trials versus observational studies), the less likely it was to report a difference in survival rates between digoxin and non-digoxin users [37].

10. Choosing More Appropriate Endpoints in HF Trials: Focus on Reducing HF Readmission Rates

Future randomised studies evaluating HF medications should probably focus on cause-specific outcomes that are anticipated to be altered by a specific therapy or intervention rather than all-cause events, which are more susceptible to spurious correlations and can be misleading [50]. This was very skillfully illustrated in an editorial by Brophy [51] commenting on the paradox observed in the second International Study of Infarct Survival (ISIS-2) trial, where the subgroup of patients with a Libra or Gemini zodiacal sign appeared not to benefit from aspirin after myocardial infarction.

The 30-day hospital readmission rate still stands at an alarming 20 % [52] despite significant advancements in HF therapy, the adoption of national standards, and fines demanding strict adherence to guidelines. Vaduganathan et al. [53] claim that hemodynamic abnormalities rather than actual disease progression are more likely to blame for this elevated early risk of readmission. Digoxin's method of action is reflected in the fact that it raises EF and cardiac output while decreasing pulmonary capillary wedge pressure [7]-[9]. Digoxin, unlike beta-blockers, ACEi, or ARB, can be safely administered to people with borderline blood pressure since it decreases heart rate and has no effect on blood pressure. Digoxin, unlike renin-angiotensin-aldosterone system inhibitors, can be used in patients with marginal kidney function without running the risk of further renal impairment. Digoxin was also linked to 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.

When given as an adjuvant drug on top of disease-modifying, life-prolonging HF treatment with the aim of lowering hospitalizations, digoxin may be very important in this respect. In a subset of 3,405 DIG patients 65 years of age or older with a reduced EF, digoxin therapy was associated with a 44 % relative risk decrease in 30-day all-cause and HF-related hospitalization rates compared to placebo [55]. These results should be interpreted cautiously, though, as this substantial influence was more pronounced in a subset of those who were using chronic digoxin medication and hence more likely to go worse after the medicine was removed.

11. Why Patients are Mostly Responding to Digoxin?

A cluster analysis of the original DIG population data revealed that female gender, hypertension, and a relatively preserved EF were among the clinical traits of patients who appeared to receive less benefit or even harm from digoxin therapy, which meant no reduction in HF-related admissions or an increase in all-cause mortality. On the other hand, patients with systolic dysfunction and S3 gallop had lower systolic blood pressure, fewer hospital admissions, and no increased mortality [56]. In keeping with this, digoxin treatment was linked to a lower incidence of the combined endpoints of HF-related mortality and hospitalisation at 2 years when compared to placebo in the three high-risk groups identified by the DIG protocol, namely those with NYHA class III-IV symptoms and cardiothoracic ratio > 55 % or EF 25 % [39].

12. Conclusion

In conclusion, the clinician must decide between high-quality information from clinical trials that were carried out more than 20 years ago, before modern HF therapy was available, and weaker information that comes mainly from observational

studies and post-hoc analyses, though it does include current HF populations. Realistically, it is doubtful that another clinical research of the scope of the DIG will be financed given the lack of corporate support. However, we believe that cardiac glycosides should not be completely excluded from the HF toolbox. Digoxin is likely to be beneficial for patients with severe HF and congestion symptoms who are unable to take high doses of drugs that treat the condition because of borderline renal or blood pressure functions. Digoxin should be used to lower hospital readmissions while reducing the risk of toxicity, and SDC, creatinine, and potassium levels should be periodically checked.

References

[1] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.

[2] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology - developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-1847.

[3] Cox JL, Ramer SA, Lee DS, Humphries K, Pilote L, Svenson L, Tu JV: Pharmacological treatment of congestive heart failure in Canada: a description of care in five provinces. Can J Cardiol 2005;21:337-343.

[4] Wasserstrom JA, Aistrup GL: Digitalis: new actions for an old drug. Am J Physiol Heart Circ Physiol 2005;289:H1781-H1793.

[5] Sagawa T, Sagawa K, Kelly JE, Tsushima RG, Wasserstrom JA: Activation of cardiac ryanodine receptors by cardiac glycosides. Am J Physiol Heart Circ Physiol 2002;282:H1118-H1126.

[6] Fedida D, Noble D, Rankin AC, Spindler AJ: The arrhythmogenic transient inward current iTI and related contraction in isolated guinea-pig ventricular myocytes. J Physiol 1987;392:523-542.

[7] Gheorghiade M, Hall VB, Jacobsen G, Alam M, Rosman H, Goldstein S: Effects of increasing maintenance dose of digoxin on left ventricular function and neurohormones in patients with chronic heart failure treated with diuretics and angiotensin-converting enzyme inhibitors. Circulation 1995;92:1801-1807.

[8] Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn PA, Eichhorn EJ: Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? J Am Coll Cardiol 1997;29:1206-1213.

[9] Gheorghiade M, Hall V, Lakier JB, Goldstein S: Comparative hemodynamic and neurohormonal effects of intravenous captopril and digoxin and their combinations in patients with severe heart failure. J Am Coll Cardiol 1989;13:134-142.

[10] Newton GE, Tong JH, Schofield AM, Baines AD, Floras JS, Parker JD: Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. J Am Coll Cardiol 1996;28:155-161.

[11] Brouwer J, van Veldhuisen DJ, Man in ‘t Veld AJ, Dunselman PH, Boomsma F, Haaksma J, Lie KI: Heart rate variability in patients with mild to moderate heart failure: effects of neurohormonal modulation by digoxin and ibopamine. The Dutch Ibopamine Multicenter Trial (DIMT) Study Group. J Am Coll Cardiol 1995;26:983-990.

[12] Krum H, Bigger JT Jr, Goldsmith RL, Packer M: Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. J Am Coll Cardiol 1995;25:289-294.

[13] Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienzle MG: Sympathoinhibitory responses to digitalis glycosides in heart failure patients: direct evidence from sympathetic neural recordings. Circulation 1989;80:65-77.

[14] Heesch CM, Abboud FM, Thames MD: Acute resetting of carotid sinus baroreceptors. 2. Possible involvement of electrogenic Na+ pump. Am J Physiol 1984;247:H833-H839.

[15] Gheorghiade M, Ferguson D: Digoxin: a neurohormonal modulator in heart failure? Circulation 1991;84:2181-2186.

[16] Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK: Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors: RADIANCE study. N Engl J Med 1993;329:1-7.

[17] van Veldhuisen DJ, Brouwer J, Man in ‘t Veld AJ, Dunselman PH, Boomsma F, Lie KI: Progression of mild untreated heart failure during six months follow-up and clinical and neurohumoral effects of ibopamine and digoxin as monotherapy. DIMT Study Group. Dutch Ibopamine Multicenter Trial. Am J Cardiol 1995;75:796-800.

[18] Lee DC, Johnson RA, Bingham JB, Leahy M, Dinsmore RE, Goroll AH, Newell JB, Strauss HW, Haber E: Heart failure in outpatients: a randomized trial of digoxin versus placebo. N Engl J Med 1982;306:699-705.

[19] van Veldhuisen DJ, Man in ‘t Veld AJ, Dunselman PH, Lok DJ, Dohmen HJ, Poortermans JC, Withagen AJ, Pasteuning WH, Brouwer J, Lie KI: Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMT). J Am Coll Cardiol 1993;22:1564-1573.

[20] Hopper I, Skiba M, von Lueder TG, Watanabe M, Funston R, Tonkin A, Krum H: Digoxin withdrawal worsens clinical status in stable patients with heart failure receiving optimal contemporaneous therapy - a randomized controlled trial. J Card Fail 2015;21:779-781.

[21] Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK: Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol 1993;22:955-962.

[22] Adams KF Jr, Gheorghiade M, Uretsky BF, Patterson JH, Schwartz TA, Young JB: Clinical benefits of low serum digoxin concentrations in heart failure. J Am Coll Cardiol 2002;39:946-953.

[23] The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525-533.

[24] Rathore SS, Wang Y, Krumholz HM: Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002;347:1403-1411.

[25] Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM: Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003;289:871-878.

[26] Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, Gheorghiade M: Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol 2005;46:497-504.

[27] Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS, Adams KF, Gheorghiade M: Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J 2006;27:178-186.

[28] Domanski M, Fleg J, Bristow M, Knox S: The effect of gender on outcome in digitalis-treated heart failure patients. J Card Fail 2005;11:83-86.

[29] Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M: Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006;114:397-403.

[30] Dhaliwal AS, Bredikis A, Habib G, Carabello BA, Ramasubbu K, Bozkurt B: Digoxin and clinical outcomes in systolic heart failure patients on contemporary background heart failure therapy. Am J Cardiol 2008;102:1356-1360.

[31] Georgiopoulou VV, Kalogeropoulos AP, Giamouzis G, Agha SA, Rashad MA, Waheed S, Laskar S, Smith AL, Butler J: Digoxin therapy does not improve outcomes in patients with advanced heart failure on contemporary medical therapy. Circ Heart Fail 2009;2:90-97.

[32] Butler J, Anand IS, Kuskowski MA, Rector T, Carson P, Cohn JN: Digoxin use and heart failure outcomes: results from the Valsartan Heart Failure Trial (Val-HeFT). Congest Heart Fail 2010;16:191-195.

[33] Freeman JV, Yang J, Sung SH, Hlatky MA, Go AS: Effectiveness and safety of digoxin among contemporary adults with incident systolic heart failure. Circ Cardiovasc Qual Outcomes 2013;6:525-533.
[34] Adelstein E, Schwartzman D, Jain S, Bazaz R, Saba S: Effect of digoxin on shocks in cardiac resynchronization therapy-defibrillator patients with coronary artery disease. Am J Cardiol 2014;113:970-975.
[35] Lee AY, Kutyifa V, Ruwald MH, McNitt S, Polonsky B, Zareba W, Moss AJ, Ruwald AC: Digoxin therapy and associated clinical outcomes in the MADIT-CRT trial. Heart Rhythm 2015;12:2010-2017.
[36] Vamos M, Erath JW, Hohnloser SH: Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Eur Heart J 2015;36:1831-1838.
[37] Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D: Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015;351:h4451.
[38] Opie LH: Digitalis, yesterday and today, but not forever. Circ Cardiovasc Qual Outcomes 2013;6:511-513.
[39] Gheorghiade M, Patel K, Filippatos G, Anker SD, van Veldhuisen DJ, Cleland JG, Metra M, Aban IB, Greene SJ, Adams KF, McMurray JJ, Ahmed A: Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. Eur J Heart Fail 2013;15:551-559.
[40] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.
[41] Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, De Mets DL: Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-1658.
[42] Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-2007.
[43] Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316:1429-1435.
[44] Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293-302.
[45] Ahmed A, Pitt B, Rahimtoola SH, Waagstein F, White M, Love TE, Braunwald E: Effects of digoxin at low serum concentrations on mortality and hospitalization in heart failure: a propensity-matched study of the DIG trial. Int J Cardiol 2008;123:138-146.
[46] Wang L, Wible BA, Wan X, Ficker E: Cardiac glycosides as novel inhibitors of human ether-a-go-go-related gene channel trafficking. J Pharmacol Exp Ther 2007;320:525-534.
[47] Jelliffe RW: Some comments and suggestions concerning population pharmacokinetic modeling, especially of digoxin, and its relation to clinical therapy. Ther Drug Monit 2012;34:368-377.
[48] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-717.
[49] Cleland JG, Cullington D: Digoxin: quo vadis? Circ Heart Fail 2009;2:81-85.
[50] Yusuf S, Negassa A: Choice of clinical outcomes in randomized trials of heart failure therapies: disease-specific or overall outcomes? Am Heart J 2002;143:22-28.
[51] Brophy JM: Rehabilitating digoxin. Eur Heart J 2006;27:127-129.
[52] Bergethon KE JC, DeVore AD, Hardy NC, Fonarow GC, Yancy CW, Heidenreich PA, Bhatt DL, Peterson ED, Hernandez AF: Lack of Improvement in 30-day readmission rates for patients hospitalized with heart failure: data from Get with the Guidelines Heart Failure Registry. J Card Fail 2015;21:S10.
[53] Vaduganathan M, Fonarow GC, Gheorghiade M: Drug therapy to reduce early readmission risk in heart failure: ready for prime time? JACC Heart Fail 2013;1:361-364.
[54] Testani JM, Brisco MA, Tang WH, Kimmel SE, Tiku-Owens A, Forfia PR, Coca SG: Potential effects of digoxin on long-term renal and clinical outcomes in chronic heart failure. J Card Fail 2013;19:295-302.
[55] Bourge RC, Fleg JL, Fonarow GC, Cleland JG, McMurray JJ, van Veldhuisen DJ, Gheorghiade M, Patel K, Aban IB, Allman RM, White-Williams C, White M, Filippatos GS, Anker SD, Ahmed A: Digoxin reduces 30-day all-cause hospital admission in older patients with chronic systolic heart failure. Am J Med 2013;126:701-708.
[56] Ather S, Peterson LE, Divakaran VG, Deswal A, Ramasubbu K, Giorgberidze I, Blaustein A, Wehrens XH, Mann DL, Bozkurt B: Digoxin treatment in heart failure - unveiling risk by cluster analysis of DIG data. Int J Cardiol 2011;150:264-269.