Digoxin in Heart Failure with a Reduced Ejection Fraction: A Risk Factor or a Risk Marker?

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Key Words

Digoxin · Heart failure · Reduced ejection fraction

Abstract

Digoxin is one of the oldest compounds used in cardiovascular medicine. Nevertheless, its mechanism of action and most importantly its clinical utility have been the subject of an endless dispute. Positive inotropic and neurohormonal modulation properties are attributed to digoxin, and it was the mainstay of heart failure therapeutics for decades. However, since the institution of β -blockers and aldosterone antagonists as part of modern heart failure medical therapy, digoxin prescription rates have been in free fall. The fact that digoxin is still listed as a valid therapeutic option in both American and European heart failure guidelines has not altered clinicians' attitude towards the drug. Since the publication of original Digitalis Investigation Group trial data, a series of reports based predominately on observational studies and post hoc analyses have raised concerns about the clinical efficacy and long-term safety of digoxin. In the present review, we will attempt a critical appraisal of the available clinical evidence regarding the efficacy and safety of digoxin in heart failure patients with a reduced ejection fraction. The methodological issues, strengths, and limitations of individual studies will be highlighted.

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Introduction

Digoxin is a purified cardiac glycoside extracted from the foxglove plant, and since its original description in 1785 by William Withering it is still in clinical use. Digoxin was the cornerstone of heart failure (HF) therapy for decades until the change in paradigm in HF pathophysiology which led to a shift from inotropic support to neurohormonal modulation. Despite being widely endorsed by both American College of Cardiology Foundation/American Heart Association [1] and European Society of Cardiology [2] HF guidelines, with IIa and IIb class recommendations, respectively, the use of digoxin is constantly declining [3]. At least two factors can explain why clinicians seem reluctant to prescribe digoxin: first, there is a great deal of uncertainty regarding 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. In this narrative review, we will scrutinize the existing literature regarding the role of digoxin in the treatment of HF patients with a reduced ejection fraction (EF).

Digoxin: Mechanism of Action and Toxicity

Digoxin binds to the sarcolemmal $\text{Na}^+\text{-K}^+$ ATPase pump, thereby blocking Na^+ extrusion outside the myocyte in exchange for K^+ . Progressively accumulating Na^+ ions inside the sarcoplasm lead to a secondary increase in the intracellular Ca^{++} concentration as the $\text{Na}^+\text{-Ca}^{++}$ exchanger promotes Ca^{++} influx over efflux. Calcium is transported into the sarcoplasmic reticulum, where it is stored during diastole. When the next depolarizing impulse reaches the myocyte, a greater quantity of Ca^{++} is released, resulting in a more forceful contraction during excitation-contraction coupling [4]. Furthermore, evidence from experimental studies supports the assertion that cardiac glycosides may have a direct effect on cardiac ryanodine receptor-2 [5]. Apart from its positive inotropic action, digoxin exhibits negative chronotropic properties; the increased intracellular Ca^{++} levels lengthen phase IV and phase 0 of the cardiac action potential, thereby slowing the heart rate.

However, the same mechanism that explains the action of digoxin is probably also the one accountable for its toxicity. Progressively accumulating Ca^{++} ions eventually exceed the storing capacity of the sarcoplasmic reticulum; this stimulates the forward mode of the $\text{Na}^+\text{-Ca}^{++}$ exchanger and a transient inward depolarizing current arises. This is believed to be the electrophysiological mechanism responsible for the generation of delayed after-depolarizations, which in turn can induce polymorphic ventricular tachycardia due to triggered activity [4, 6].

Digoxin: Oral Inotrope and Neurohormonal Modulator

Digoxin has been reported to exert favorable hemodynamic effects by increasing the EF [7, 8] and cardiac index [9] and reducing the pulmonary capillary wedge pressure [9]. Intravenous digoxin administration has been demonstrated to reduce cardiac norepinephrine spillover in patients with severe HF and elevated left ventricular filling pressures [10]. In patients with chronic HF, oral digoxin therapy led to a significant drop in plasma norepinephrine levels [11, 12]. Interestingly, digitalis glycosides appear to exert a differential physiologic effect on patients with HF compared to normal subjects. Intravenous digoxin boluses produced a drop in forearm vascular resistance and a sustained decrease in efferent sympathetic nerve activity to the muscles in HF patients but not in normal subjects. This sympathoinhibitory response to di-

goxin is unrelated to its positive inotropic action since dobutamine did not have any effect on the above two indices despite a comparable increase in cardiac index [13]. Digoxin may also improve the carotid sinus baroreflex sensitivity [12] by preventing acute resetting of baroreceptors, thereby indirectly decreasing the sympathetic nerve system activity [14, 15]. Apart from its sympatholytic properties, digoxin enhances the cardiac vagal tone, which is reflected in an increase in heart rate variability [8, 11, 12]. Digoxin reduced the heart rate by an average of 4–7 bpm during sinus rhythm [16–18]. Finally, digoxin therapy has been reported to decrease the plasma renin activity [19], whereas digoxin discontinuation has been linked to a rise in plasma brain natriuretic peptide levels [20]. Of note, the beneficial neurohormonal effects of the drug are apparent even at low maintenance doses [7, 8], while further dose escalation might provide some additional inotropic support but no further decrease in neuroendocrine activation [7].

Early Randomized Clinical Trial Data

The Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) is a randomized, double-blind, placebo-controlled trial that included 88 patients with chronic HF and sinus rhythm with mild to moderate symptoms. All study participants were on diuretics and digoxin at baseline. The patients were randomized to replacement of digoxin with placebo or continuation of digoxin. Patients who discontinued digoxin experienced worsening of their maximal exercise capacity, accompanied by an increased incidence of treatment failures. On the contrary, patients allocated to the active treatment group maintained a lower body weight and heart rate and a higher EF [21].

The Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) study is a randomized, double-blind, placebo-controlled trial that included 178 chronic HF patients with New York Heart Association (NYHA) class II or III symptoms, EF <35%, and sinus rhythm. Baseline therapy included a stable dose of diuretics, digoxin, and angiotensin-converting enzyme inhibitors (ACEi). Patients were randomly assigned to continuing to receive digoxin or switching to placebo. Patients taken off digoxin experienced more often worsening of their HF status along with deterioration of their overall functional capacity; the latter was reflected by a decline in their maximal exercise tolerance and worsening of their NYHA class. Patients who stayed on

digoxin maintained a higher EF and a lower weight and heart rate [16].

In a pooled analysis of the above two studies, uninterrupted digoxin therapy was beneficial irrespective of the baseline serum digoxin concentration (SDC). Patients in the lower-SDC group were less likely to experience worsening of their HF symptoms and maintained a better exercise capacity compared to those on placebo, while there was no decline in their EF [22].

The Dutch Ibopamine Multicenter Trial (DIMIT) is a randomized, placebo-controlled trial that included 59 chronic HF patients with a mean EF of 30% and mild to moderate symptoms who were treated only with diuretics. Patients were randomized at a 1:1:1 ratio to receiving placebo or ibopamine or digoxin. After 6 months, digoxin treatment but not ibopamine was associated with a significantly increased exercise time compared to placebo [19].

The Digitalis Investigation Group Study

These early encouraging findings paved the way for a large study, i.e. the Digitalis Investigation Group (DIG) study [23]. This is a randomized, double-blind, placebo-controlled trial that included 6,800 chronic HF patients, mainly NYHA class II-III, with EF $\leq 45\%$. The participants were randomized in a 1:1 fashion to receiving either digoxin or placebo, and the primary endpoint was all-cause mortality. Of note, $>94\%$ of patients were on ACEi and $>80\%$ were receiving a diuretic. After 37 months of follow-up, there was no difference with respect to all-cause mortality between the two study groups. Patients randomized to digoxin had 6% fewer hospitalizations. Of note, digoxin was associated with relative risk reductions of 13 and 28% in hospitalization rates for a cardiovascular reason and for worsening HF compared to placebo, respectively. Moreover, there was a strong trend towards decreased mortality due to worsening HF in the digoxin arm ($p = 0.06$), but at the same time there was an increased death rate ($p = 0.04$) due to other cardiac causes – presumably arrhythmias – although the latter was not a prespecified endpoint.

Post hoc Analyses of DIG Data

In a post hoc analysis of DIG trial data, Rathore et al. [24] reported a 5.8% absolute increase in the all-cause death rate among female patients assigned to digoxin compared to their male counterparts, suggesting a sig-

nificant treatment-gender interaction. Subsequently, the same group of authors focused on male patients who were alive at 1 month post-randomization with available SDC measurements. Men with SDC in the lower range, i.e. 0.5–0.8 ng/ml, had a 20% relative risk reduction in all-cause mortality and an impressive 44% relative risk reduction in HF hospitalization rates compared to those on placebo. Conversely, patients with SDC in the upper range, i.e. ≥ 1.2 ng/ml, experienced an 11.8% absolute increase in all-cause mortality, which was significantly higher compared to patients on placebo [25].

These two observations sparked a debate regarding a possible digoxin-gender interaction and called for revision of the traditional SDC therapeutic range. However, further post hoc analyses of the DIG [26, 27] and Studies of Left Ventricular Dysfunction (SOLVD) data [28] did not replicate the findings of Rathore et al. [24] of an increased risk among women. Domanski et al. [28], reanalyzing the SOLVD data, reported that there was no evidence that women treated with digoxin did worse than their male counterparts in terms of all-cause or cause-specific mortality. However, data on SDC were not collected. Adams et al. [26] focused on a subset of DIG patients ($n = 4,944$), of both genders, alive at 1 month post-randomization who had available SDC measurements. In this population, women with SDC in the lower range, i.e. 0.5–0.9 ng/ml, had mortality rates similar to those obtained with placebo and a significant 30% relative risk reduction in HF-related hospital admissions. However, an increase in all-cause mortality – albeit of marginal statistical significance – was observed among women with SDC ranging from 1.2 to 2.0 ng/ml. A similar trend was observed among men, i.e. there was a significant reduction in both mortality and morbidity endpoints at low SDC, while all mortality advantages were attenuated at higher SDC, although the finding of reduced hospital admissions persisted [26].

Finally, Ahmed et al. [29] analyzed the data of the entire DIG population – including those enrolled into the ancillary trial – irrespective of sex and baseline EF, who were still alive at 1 month post-randomization and had SDC determined at 1 month ($n = 5,548$). After a median follow-up period 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 and 38%, respectively, compared to those on placebo. On the other hand, patients with an SDC ≥ 1 ng/ml, while still enjoying a significant 32% relative risk reduction in HF hospitalizations, had mortality rates similar to those of patients on placebo [27].

Digoxin in Contemporary HF Patients

Following the publication of the DIG trial, a series of reports on the role of digoxin on clinical outcomes in contemporary HF cohorts including patients taking ACEi/angiotensin receptor blockers (ARB) and β -blockers came to light. In an observational study, Dhaliwal et al. [30] explored the effect of digoxin on all-cause mortality and/or HF readmissions in 347 patients discharged with a diagnosis of systolic HF. These patients were on a background therapy of β -blockers and ACEi/ARB. After adjustment for a series of potentially confounding variables, digoxin therapy was not associated with a lower rate of all-cause mortality or fewer HF-related hospital admissions [30].

The efficacy and safety of digoxin were challenged once more in a retrospective study including 455 patients who were referred for transplant evaluation. It should be noted that >90% of the patients enrolled were on ACEi/ARB and β -blockers, half of them were on aldosterone antagonists and digoxin, and 60% had an implantable cardiac defibrillator in situ. After a median follow-up time of 27 months, more than twice as many digoxin-treated patients, compared to those not taking the drug, met the composite endpoint of death, urgent transplantation, or ventricular assist device implantation. Of note, no difference in all-cause or HF-related hospital admission rates was documented between the two groups [31]. In the same line were the results of a retrospective analysis of Valsartan in Heart Failure Trial (Val-HeFT) data [32]. In the original Val-HeFT study, a total of 5,010 symptomatic HF patients were enrolled, 3,374 (67%) of whom were on digoxin at baseline. After adjustment for baseline between-group differences, digoxin treatment was associated with a higher risk of all-cause mortality and HF-related hospitalizations [32].

More recently, the effect of digoxin on all-cause mortality and HF hospitalizations was evaluated in a large ($n = 2,891$) cohort of patients with newly diagnosed systolic HF. At baseline, about half of the patients were on ACEi/ARB and a similar percentage was on β -blockers, while almost 20% were prescribed digoxin for the first time (incident digoxin users). Over a median follow-up of 2.5 years, patients treated with digoxin showed a 72% increase in the relative risk of death compared to non-digoxin users after multivariate adjustment for baseline between-group differences. Moreover, no difference in HF hospitalization rates was identified [33].

Adelstein et al. [34] explored the effect of digoxin on appropriate implantable cardioverter defibrillator thera-

pies in 350 patients with ischemic heart disease who received a cardiac resynchronization therapy defibrillator for primary prevention according to current guidelines. After implantation, 46% of the study participants were discharged on digoxin and the mean follow-up time was 48 months. The time to the first appropriate shock was significantly shorter among digoxin-treated patients, while there was no difference in the rates of appropriate antitachycardia pacing therapies. Of note, the digoxin proarrhythmic effect was more pronounced among those with an EF <22%.

The above findings were further supported by a post hoc analysis of Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) data. At baseline, 26% of the patients were on digoxin. The 4-year cumulative probability of death was not significantly different between digoxin users and nonusers. The same was true for HF hospitalization rates and the combined endpoint of death or HF-related hospital admission. However, digoxin use was associated with a significant 41% increase in the relative risk of ventricular tachycardia/fibrillation, which was mainly driven by a 65% increase in the relative risk of high-rate episodes ≥ 200 beats/min [35].

Meta-Analyses Evaluating the Role of Digoxin

In a meta-analysis by Vamos et al. [36], 19 reports were identified regarding the effect of digoxin on all-cause mortality in patients with atrial fibrillation, HF, or both. In 9 studies, in which only HF patients were included ($n = 91,379$), digoxin use was associated with a small, albeit significant, 14% increase in the relative risk of all-cause mortality [36]. In another meta-analysis conducted by Ziff et al. [37], the opposite conclusion was reached. A total of 52 studies were reviewed, pooling data from 621,845 patients. The death risk ratio was increased for digoxin users in unadjusted and adjusted analyses and in propensity-matched cohorts, but it was neutral in randomized controlled trials. In particular, when analyzing data from 7 randomized controlled trials pooling data from 8,406 patients, no difference with respect to all-cause mortality between those randomized to digoxin and those on placebo could be detected. Moreover, irrespective of the study design, digoxin led to a small, albeit significant, relative risk reduction of 8% in all-cause hospital admissions.

Discussion

Criticism of PROVED and RADIANCE

PROVED [21] and RADIANCE [16] enrolled ambulatory HF patients who were stable on chronic digoxin therapy and were randomized to either continuing on digoxin or switching to placebo. Withdrawal studies, however, cannot provide a definite answer regarding whether a certain treatment was necessary in the first place. Moreover, in studies with a similar design, the efficacy of the drug under investigation is often overstated. Patients, who were stable on digoxin prior to entering the study are more likely to deteriorate upon its removal from their drug regimen. Finally, in both studies a limited number of patients were enrolled, there was a short follow-up period, and no hard endpoints were assessed.

Scrutinizing the DIG Trial

The DIG [23] study is a large, multicenter, randomized, double-blind, placebo-controlled trial in which 6,800 chronic HF patients were randomized to receiving either digoxin or placebo. The median follow-up time extended beyond 3 years and the primary endpoint used was the hardest available, i.e. all-cause mortality. Overall, 3 aspects of the DIG trial have attracted the most of the scrutiny: the patient enrollment process, the background medical therapy, and the digoxin dose.

Looking at DIG population baseline data, it is clear that 44.1% of the patients assigned to digoxin were already on digoxin before study entry, while 44.6% of the patients allocated to placebo were previously on stable, chronic digoxin therapy. Of note, all of these patients entered the study without a wash-out period. Thus, for about a quarter of the DIG participants this was a digoxin withdrawal study, while for another quarter of them the prevalent rather than the incident digoxin therapy was assessed. In a very interesting editorial, Opie [38] cast serious doubts on whether the DIG study would have yielded the same results if digoxin had been added on top of ACEi and diuretics in truly digoxin-naïve patients [38].

The second major drawback, limiting the applicability and generalizability of the DIG trial results in contemporary HF patients, has to do with the background therapy of the study participants. The DIG trial was conducted in the early nineties; at that time β -blockers and aldosterone antagonists were not used routinely in HF patients while device-based therapy was not an option either. Gheorghiade et al. [39], in an attempt to defend the case for digoxin and the applicability of the DIG results, noted that β -blocker studies [40–42] were conducted on popula-

tions with high background use of digoxin and that one could argue that β -blockers may be ineffective in the absence of digoxin. In the same line, early clinical trials, which established the role of ACEi in HF, were conducted in the pre- β -blocker era [43, 44]; however, ACEi are still considered the cornerstone of HF therapy.

Finally, a third weak spot in the DIG trial is related to digoxin dose. The median daily digoxin dose was 250 μ g since, in the period during which the study was conducted, SDC of up to 2 ng/ml were considered therapeutic. Later, however, it became apparent that SDC >1 ng/ml were associated with worse outcomes and the optimal SDC range was amended down to 0.5–0.9 ng/ml [27]. Admittedly, maintaining SDC within such a narrow range can be quite challenging in real-life patients. One should bear in mind that typical patients with advanced HF are elderly, have impaired renal function and other comorbidities, and are taking concomitant medications that may either directly impair kidney function (e.g. ACEi/ARB) or indirectly increase digoxin levels due to drug-drug interactions (e.g. via P-glycoprotein inhibition). In a subpopulation of the DIG trial, it was demonstrated that a daily digoxin dose $\leq$ 125 μ g was the strongest independent predictor of a low SDC (e.g. 0.5–0.9 ng/ml) [45].

Adding a further layer of complexity to the optimal-SDC debate, experimental evidence supports the assertion that cardiac glycosides can block the rapid component of a delayed potassium rectifier current even at nanomolar concentrations [46]. This could lead to action potential prolongation, thereby predisposing cardiac myocytes to electrical instability via the same mechanism as class III Vaughan-Williams antiarrhythmic drugs. Moreover, digoxin is distributed not only in plasma but also in the peripheral nonserum compartment; it has also been suggested that the clinical effects and toxicity of digoxin may not be related to its plasma levels, and thus tailoring the digoxin dose based on the SDC could be misleading [47].

Sadly, there are no clinical trials designed specifically to test the hypothesis of whether the adoption of lower SDC actually translates into a lower arrhythmic risk. Theoretically, contemporary HF drugs, including β -blockers and spironolactone, both of which help to maintain adequate potassium levels, might also aid in the reduction of digoxin-related proarrhythmia. The latter view is supported by the results of a prespecified subgroup analysis in the Randomized Aldactone Evaluation Study (RALES), where spironolactone reduced the all-cause mortality compared to placebo only among those who were on background digoxin therapy [48]. Of note, in the RALES more than 70% of patients enrolled in both arms were on digoxin.

Observational Studies and post hoc Analyses: How Much Can We Rely on Them?

Observational Studies

An inherent disadvantage of the observational studies discussed earlier [30, 31, 33, 34] is that, by definition, treatment assignment is not the result of any randomization process. Statistical adjustments notwithstanding, the possibility of residual confounding due to unmeasured variables cannot be ruled out. In the study by Dhaliwal et al. [30], patients discharged on digoxin had a more severe left ventricular systolic dysfunction, a higher prevalence of atrial fibrillation, and more previous admissions due to worsening HF, and they were less likely to be hypertensive; hence, the risk of confounding by indication is likely. In the Kaiser Permanente Northern California database, a relatively large, diverse, community-based patient cohort with newly diagnosed HF was identified [33]. The effect of incident digoxin use was studied, avoiding the caveat of assessing outcomes in relation to the prevalent therapy. Also, digoxin use was treated as a time-dependent variable, which means that a certain outcome could be assigned to digoxin only if the patient was on digoxin during the period in which the event actually occurred. However, data on the patients' characteristics and outcomes were retrospectively collected. Moreover, as in any observational study, there is always the unavoidable risk of assessing outcomes on treatment rather than answering a more clinically relevant question, i.e. evaluation of the response to a certain therapy [33]. In simple words, if a patient who is destined to have a good prognosis is treated with an unnecessary medication, then an external observer would credit a patient's good outcome to the drug despite there being no causal link between the two.

Post hoc Analyses

Similar to the studies with an observational design, post hoc analyses of randomized clinical trial data [32, 35] share a common feature: digoxin treatment per se is not randomized. Hence, the argument that digoxin could have been reserved for sicker patients – who would have had a worse prognosis anyway – is plausible. In the Val-HeFT post hoc analysis [32], patients on digoxin were more symptomatic, had lower a EF and blood pressure, and were less likely to be on concomitant β -blocker therapy. The same applies to the MADIT-CRT post hoc analysis, in which, according to the authors, despite extensive adjustment for baseline between-group differences, the possibility of residual confounding could not be ruled out [35]. According to Ziff et al. [37], prescription bias against digoxin appears to be very common. An obvious explana-

tion is that digoxin is currently considered a second-line treatment for both HF and atrial fibrillation indications; hence, this drug is reserved for patients in whom first-line treatments have already failed.

Propensity Score Matching

Propensity score matching is a technique which is employed to reduce bias in the assessment of treatment effects by accounting for the covariates that predict reception of the treatment in the first place. It could be described as an attempt to mimic randomization by matching two groups of people based on a number of characteristics in order to make them more comparable. An obvious limitation of this method is that only differences in the measured covariates can be balanced. In a state-of-the-art editorial, Cleland and Cullington [49] highlighted the potential pitfalls inherent to propensity matching, especially when applied in assessing the effect of a drug that improves a series of parameters which on their own portend a better prognosis. As Cleland and Cullington [49] very elaborately illustrated, a patient whose EF is increased following digoxin treatment will be matched to a patient with a comparable EF without digoxin; if both patients experience an uneventful course during follow-up, then the beneficial effect of digoxin will be masked by the improvement in EF. Moreover, the application of propensity matching requires large samples and a significant overlap between the treatment and control groups; otherwise, the risk of matching the worst cases in the treatment group to individuals with the best set of characteristics in the control group or vice versa is likely.

Meta-Analyses

Inarguably, meta-analysis represents the most robust analytical tool available to extract high-quality information, graded as level-of-evidence A in guidelines documents. However, the reliability and robustness of meta-analysis results are highly dependent on the quality of the raw data contributed by each individual study. In the 52 studies that Ziff et al. [37] included in their meta-analysis, patients on digoxin were sicker and had a higher use of diuretics, suggesting 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 was (i.e. randomized controlled trials vs. observational studies) the lower the probability of reporting a difference in survival rates between digoxin and non-digoxin users was [37].

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

It has been suggested that future randomized studies evaluating HF therapies should probably include cause-specific outcomes that are expected to be affected by a certain therapy/intervention rather than all-cause events; the latter are considered to be more susceptible to spurious correlations and can be misleading [50]. This was very elegantly exemplified in an editorial by Brophy [51] commenting on the paradox observed in the second International Study of Infarct Survival (ISIS-2) trial, in which the subgroup of patients with a Libra or Gemini zodiacal sign appeared not to benefit from aspirin following myocardial infarction.

Despite the major advances that have been accomplished in HF therapy and the national standards and penalties that have been established mandating the strict implementation of guidelines, 30-day hospital readmission rates are still at the staggering figure of 20% [52]. According to Vaduganathan et al. [53], this increased early risk of readmission is not due to actual disease progression but it is more likely due to hemodynamic abnormalities. As a reflection of its mechanism of action, digoxin increases the EF and cardiac output and at the same time lowers the pulmonary capillary wedge pressure [7–9]. Digoxin lowers the heart rate and has a neutral effect on blood pressure; hence, unlike β -blockers and ACEi/ARB, it can be safely administered to patients with borderline blood pressure. Moreover, in a subset of DIG patients, digoxin was associated with an improvement in renal function defined as an increase of more than 20% in the estimated glomerular filtration rate [54]; therefore, unlike renin-angiotensin-aldosterone system inhibitors, it can be used in patients with marginal kidney function without the risk of further renal impairment.

From this perspective, digoxin may have an important role to play when used as an adjunctive agent on top of disease-modifying, life-prolonging HF therapies, aiming to reduce the hospitalization burden. In a subset of 3,405 DIG patients aged ≥ 65 years with a reduced EF, digoxin use was associated with an impressive relative risk reduction of 44 and 60% compared to placebo in 30-day all-cause and HF-related hospitalization rates, respectively [55]. However, these results should be interpreted with caution as this striking effect was more pronounced in the subset of patients who were on chronic digoxin therapy and were hence more likely to deteriorate upon digoxin withdrawal.

Patients Most Likely to Respond Favorably to Digoxin

In a cluster analysis of original DIG population data, the clinical characteristics of the patients who seemed to derive less benefit or even harm from digoxin therapy, which means no decrease in HF-related admissions or an increase in all-cause mortality, included female gender, hypertension, and a relatively preserved EF. On the other hand, sicker patients with evidence of congestion, S3 gallop, a lower systolic blood pressure, and more severe systolic dysfunction faced fewer hospital admissions and no excess mortality [56]. In the same line, in the 3 DIG protocol-prespecified high-risk groups, i.e. NYHA class III–IV symptoms and cardiothoracic ratio $>55\%$ or EF $<25\%$, digoxin treatment was associated with a lower incidence of the combined endpoints of HF-related mortality/hospitalization and all-cause death/hospitalization at 2 years compared to placebo [39].

Conclusions

In summary, the clinician faces the dilemma of relying on either high-quality data, stemming from clinical trials conducted over 2 decades ago and before modern HF therapy was available, or less-strong evidence, mainly from observational studies and post hoc analyses, albeit including contemporary HF populations. Realistically, given the lack of industry support, it is unlikely that another clinical trial of the magnitude of the DIG will be sponsored. Nevertheless, in our view, cardiac glycosides should not be discarded from the HF armamentarium. Digoxin probably still plays a role in patients with severe HF with evidence of congestion who are unable to tolerate high doses of disease-modifying agents due to borderline blood pressure/renal function. Digoxin should be used with the aim of reducing hospital readmissions, while SDC and creatinine and potassium levels should be closely monitored to minimize the risk of toxicity.

Conflict of Interest

None.

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