European Heart Journal (2017) **38**, 2095–2099
doi:10.1093/eurheartj/ehw577

CURRENT OPINION

Assumption versus evidence: the case of digoxin in atrial fibrillation and heart failure

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Received 19 April 2016; revised 17 June 2016; editorial decision 9 November 2016; accepted 18 November 2016; online publish-ahead-of-print 8 January 2017

Background

Despite development of new and innovative medical therapies, still millions of patients with chronic heart failure (HF) with reduced ejection fraction and/or atrial fibrillation (AF) are treated with cardiac glycosides (overall 122 millions of patients defined daily dose prescriptions 2013 in Germany).[1] Randomized evidence for efficacy of this treatment strategy is, however, sparse. For HF with reduced ejection fraction (HFrEF), the only randomized controlled outcome trial (RCT) of reasonable size is the DIG trial.[2] Although the DIG Trial could not demonstrate a benefit on total mortality in the overall trial population, hospitalization for worsening of HF was significantly reduced. Moreover, subgroup analysis suggested a benefit on total mortality in patients with low plasma levels of digoxin.[3,4] Randomized controlled outcome trials prospectively investigating the impact of digoxin on mortality and morbidity in patients with AF are not available. In the very recent past, quite a number of cohort studies, *post hoc* analyses of RCTs (initiated to investigate other treatments), and meta-analyses,[5–11] which are all liable to prescription bias as randomization was not targeting digoxin therapy,[12] retrospectively investigated whether digoxin treatment would eventually increase mortality in AF. These analyses surely are invaluable sources to generate important hypotheses to be investigated in prospective RCTs, which are costly, time consuming, and in need of high resources. However, it is very important to interpret their results with caution, and potential sources of bias require careful assessment and discussion.

Mortality and digoxin treatment—conflicting results in retrospective analyses

The AFFIRM study originally investigated survival outcome of patients with AF randomized to treatment for either rate (defined as therapy with beta blocker, calcium-channel blocker, digoxin, and combinations of these drugs) or rhythm control (antiarrhythmic drug use upon discretion of the treating physician).[13] Rhythm control did not offer advantages over rate control. In a first *post hoc* analysis of AFFIRM, digoxin treatment was associated with an increased all-cause mortality even after correcting for available differences in clinical characteristics and comorbidities, independent of gender or presence of HF.[6] In contrast, a second *post hoc* analysis based on the same AFFIRM study population, published back to back in the *European Heart Journal*, found no evidence of an increased mortality or hospitalization in patients with AF treated with digoxin.[5] The authors of the second analysis argued that the first *post hoc* analysis suffered from two types of bias regarding digoxin use: no randomly assigned time-dependent treatment and imbalance in covariates/populations. Therefore, these authors restricted on patients with information available on digoxin use at baseline and treated digoxin use as a fixed covariate. Furthermore, propensity matched pairs were selected, forcing balance in co-variates included in propensity matching. This more cautious analysis found no evidence of an increased mortality.[5] A third analysis of the AFFIRM study population even found a decrease in mortality by digoxin treatment in patients with an ejection fraction < 30%.[14] These inconsistent results from the same study population nicely illustrate the caveats of retrospective analyses that are most likely biased by different assumptions and statistical methods (*Figure 1*). Clearly, all three *post hoc* analyses can only be hypothesis generating and must be interpreted with extreme caution.

Similarly, retrospective analysis of other trials regarding this topic demonstrated conflicting results: RACE II was a randomized controlled open label trial designed to investigate a composite of death from cardiovascular causes and other clinically relevant events in AF patients treated with either a strict or a lenient rate control protocol. *Post hoc* analysis of RACE II indicated no increase in mortality in AF patients treated with digoxin.[7] *Post hoc* analysis of ROCKET-AF, originally comparing efficacy of rivaroxaban and

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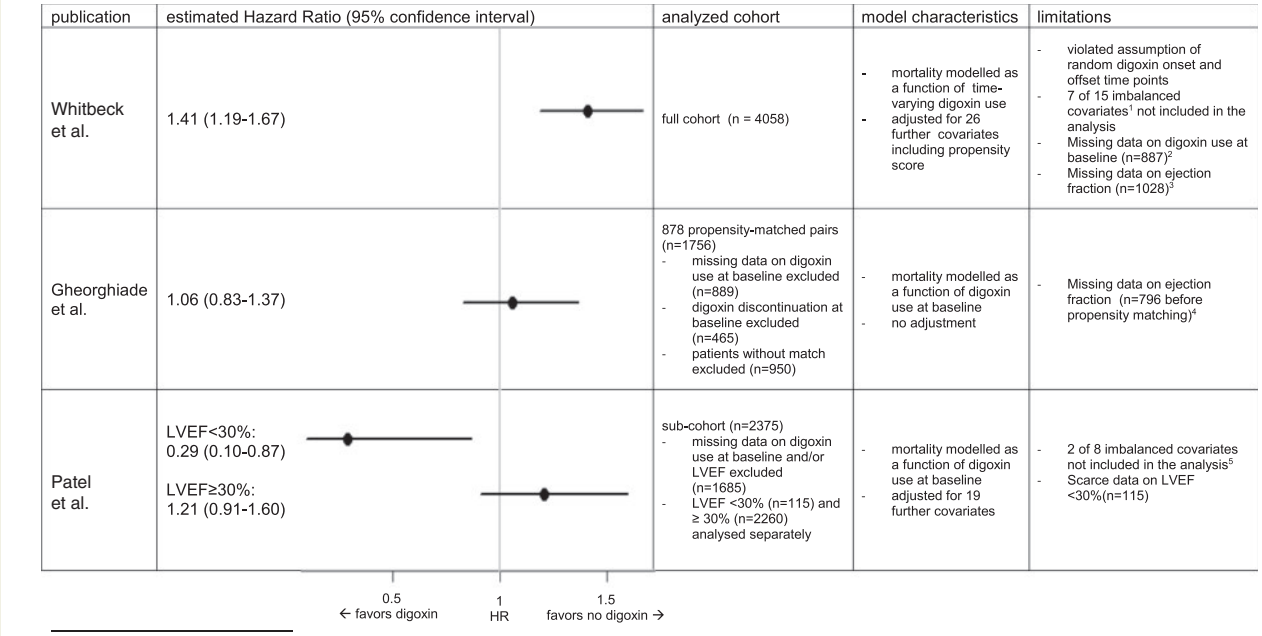

[1] Imbalanced covariates defined as having p-Value p<0.1 when comparing patients on or off digoxin within 6 months before randomization. Imbalanced but not adjusted for: oestrogen/progesterone, lipid-lowering therapy, symptoms during AF, failure of antiarrhythmic drug prior to randomization, recurrent episodes of AF prior to randomization, sotalol as initial therapy, class I drug as initial therapy

[2] digoxin use 6 months prior to randomization was used instead

[3] patients with missing ejection fraction and no history of heart failure were classified as intermediate heart failure

[4] Ejection fraction was not included in the propensity model

[5] Imbalanced covariates defined as having p-Value p<0.1 in either subgroup (EF <30% or ≥ 30%) when comparing patients on or off digoxin at baseline. Imbalanced but not adjusted for: NYHA, amiodarone

Figure 1 Results of three *post hoc* analyses of the AFFIRM trial: the modelled effect of digoxin on mortality is harmful, neutral, or beneficial, depending on the chosen analysis model.

warfarin in AF on a combined endpoint of stroke or systemic embolism,[15] indicated that digoxin might increase mortality in AF patients using different statistical models to adjust for observed population differences.[11] Furthermore, two recent retrospective cohort studies from a US as well as Taiwanese healthcare system database demonstrated an increased mortality associated with digoxin treatment in AF patients.[8,9] This association persisted after different ways of adjustment for relevant confounders (multivariate analysis and propensity matching). In sharp contrast, two very recent analyses of a French and US cohort with AF including patients with and without HF did not find any association between digoxin treatment and a change in mortality after adjustment for confounders with different models or propensity scoring.[16,17] In a Danish population-based analysis, even a decrease in mortality by digoxin treatment has been shown.[18]

Prescription bias mimics digoxin-driven mortality

Overall, in the retrospectively analysed study populations described digoxin-treated patients had significantly more comorbidities. This indicates a significant prescription bias caused by the fact that sicker patients, having a higher mortality risk *per se*, receive additional treatment with digoxin and it is a matter of belief, whether all statistical adjustments done, can truly outbalance this non-comparable baseline risk.

Finally, a recently published meta-analysis by Vamos *et al.*[10] suggested an association between digoxin treatment and overall mortality particularly in patients suffering from AF and/or HF. However, this meta-analysis included only one randomized controlled (double-blinded) clinical trial designed to investigate the effect of digoxin on mortality,[2,19] the DIG trial, which actually excluded patients with AF. All other information comes from aforementioned comparisons of summary information from very heterogeneous studies and non-experimental observational data (carrying a high risk of bias) despite methodologists recommend that combination of observational studies should be done on the basis of original patient data, only.[20,21]

To clarify the uncertainty about adverse outcomes with digoxin treatment in AF and/or HF due to conflicting results, another comprehensive meta-analysis including an even larger number of all available observational and experimental studies was performed,[12] which differentiated between results of different statistical models and excluded time-dependent analysis. This analysis demonstrated that studies with better methods and low risk of prescription bias overall report a neutral association of digoxin with mortality and a reduced rate of all cause hospitalization. In contrast, studies exhibiting a higher risk of prescription bias reported a stronger association with all-cause mortality, regardless of statistical analysis (*Figure 2*).

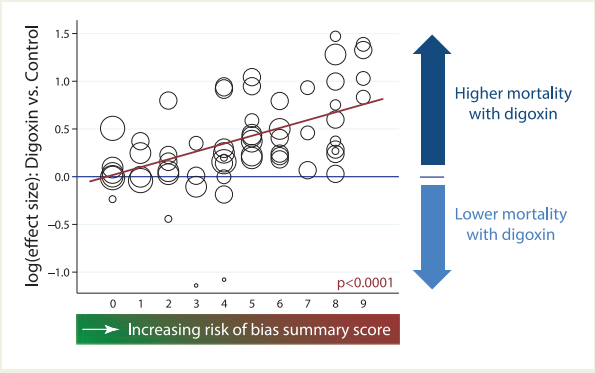

Figure 2 Impact of unrecognized treatment bias on all-cause mortality in studies investigating mortality for digoxin vs. control in randomized as well observational studies. Each circle represents a particular study with circle size dependent on the precision of each estimate in random-effects-model (reproduced by Ziff *et al.*[12], version supplied by D. Kotecha).

Knowledge of digoxin levels for proper risk adjustment in *post hoc* analyses

Because digoxin levels were not available in any of the *post hoc* analyses described, it is impossible to properly adjust risk for digoxin serum concentrations and to understand potentially underlying mechanisms attributable to digoxin as previously discussed,[22] regardless of statistical methods used to correct for relevant confounders and besides the risk of prescription bias. This risk adjustment is of high interest since data from the DIG trial indicated a reduced mortality within digoxin serum concentrations of 0.5–0.9 ng/mL and an increased mortality at serum levels above 1.0 ng/mL.[3,4] Especially in the AFFIRM study population with a chosen target serum concentration of digoxin above 1.0 ng/mL to achieve rate control, this would have been important for proper risk adjustment. In contrast, investigators in RACE II (no increase in mortality with digoxin) were not encouraged to pursue high digoxin levels although medical treatment was up-titrated to achieve rate control criteria.

In the DIG trial, digoxin dosing was determined according to an algorithm taking into account age, sex, weight, and renal function.[2] In addition, in real clinical practice, potential drug interactions as well as circumstances changing digitalis sensitivity (e.g. hypokalaemia) also have to be reflected to avoid digitalis toxicity or side effects, which can be challenging.[23] Because of the primarily renal excretion of digoxin, dose adjustment is important especially in patients with impaired renal function to avoid increases in digoxin serum concentrations driving mortality.[4] Even if statistical methods adjust for increased risk due to impaired renal function at baseline or during follow-up, this most likely does not reflect the effect of high digoxin serum levels due to impaired renal excretion, because impaired renal function and high digoxin serum levels are considered to independently drive mortality in these patients. Therefore, knowledge of digoxin serum levels could be crucial for proper risk adjustment and interpretation.

Publication bias of negative data in the media endanger patient safety and trial conduct

Of note, scientific articles of retrospective analyses indicating an increased mortality with digoxin treatment have been reported in the media and lay press. Unfortunately, these are not properly balanced with scientific publications indicating no increase in mortality by digoxin. Although they all end in mandating the conduct of randomized clinical trials,[6,8–11] these 'negative' articles and especially corresponding reports positioned in the media and lay press hinder recruitment to proper studies that are able to finally answer under controlled conditions and close supervision of patients, whether treatment with cardiac glycosides, as currently applied by many physicians, really is beneficial to patients. Furthermore, these publications might even trigger inappropriate termination of treatment with cardiac glycosides and endanger patients being in a stable clinical condition.[24] Risks are well known, and currently there is no evidence of an increased risk with cardiac glycoside treatment in the only available prospective and randomized clinical trial investigating this population, the DIG trial.[2,19]

Prospective clinical trials with cardiac glycosides initiated

Overall, prospective randomized clinical trials to properly determine the impact of cardiac glycosides on mortality and morbidity in patients with AF and/or HF are urgently needed. These clinical trials have already been initiated after successful application for public funding as there is no interest of financial support by the pharmaceutical industry. These trials will finally enable to base clinical decisions relating to patient treatment with cardiac glycosides on high quality data rather than on *post hoc* or observational data:

RATE-AF (University of Birmingham/UK, funded by UK Dept. of Health) is powered to detect a difference in quality of life comparing digoxin to beta-bockers as initial rate control therapy in permanent AF. In addition, RATE-AF is a feasibility study to plan a future major randomized controlled event-driven clinical outcome trial (https://clinicaltrials.gov/ct2/show/NCT02391337, 24 November 2016).

DIGIT-HF (Hannover Medical School/Germany, funded by Federal Ministry of Education and Research [BMBF]), a prospective, randomized clinical outcome trial, investigates the hypothesis that digitoxin—at serum concentrations in the lower therapeutic range controlled for in all patients—reduces mortality and morbidity in patients with advanced chronic systolic HF (https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-005326-38/DE, 24 November 2016). DIGIT-HF has already been initiated with public funding from the German Federal Ministry for Research and Education and is currently recruiting patients and open for further centres interested to participate.

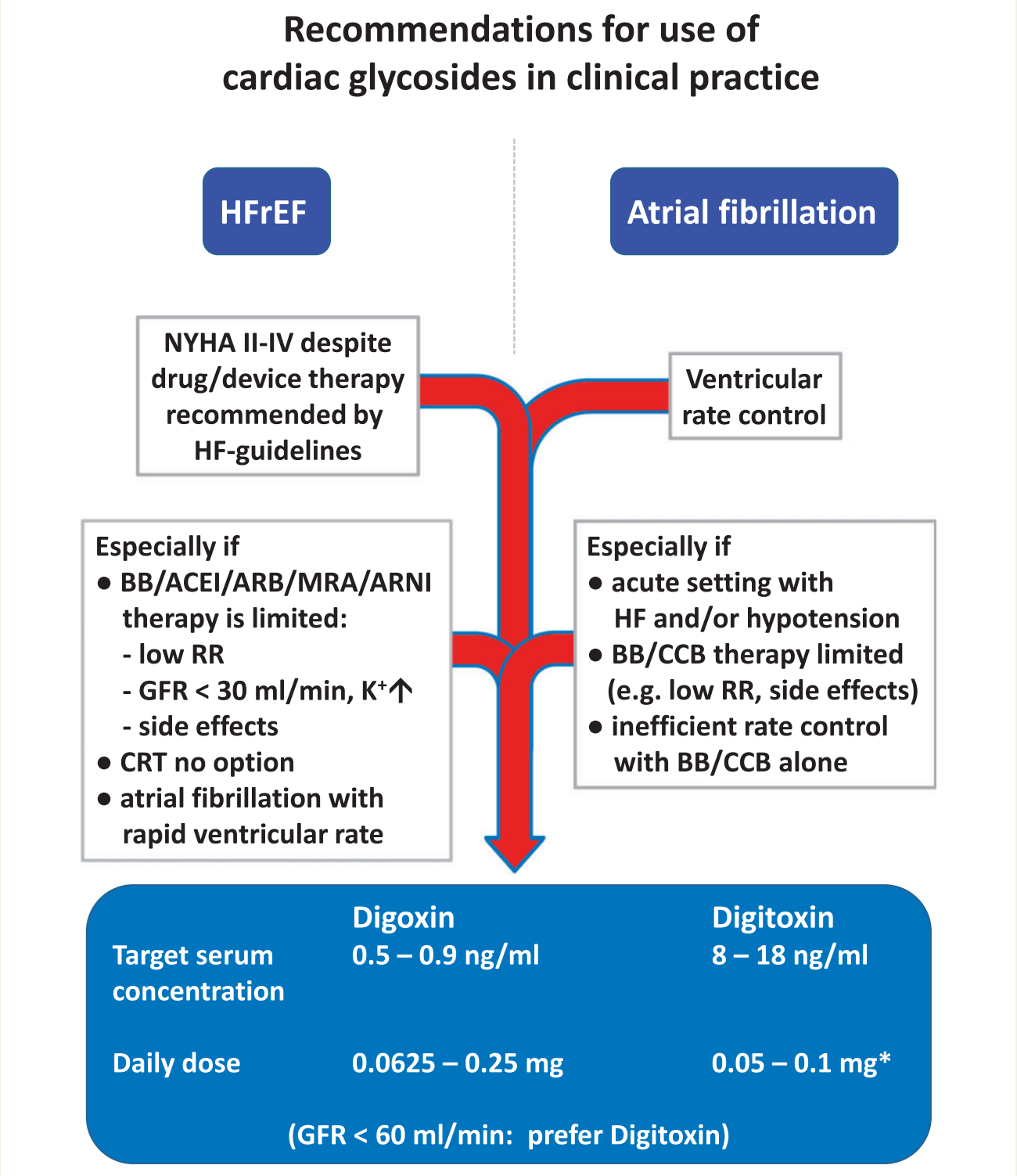

Figure 3 Recommendations for the use of cardiac glycosides in clinical practice for the treatment of heart failure with reduced ejection fraction (HFrEF) and/or atrial fibrillation (AF). Therapy with cardiac glycosides should be preferred in certain populations and target serum concentrations for digoxin and digitoxin should be in the lower part of the so called 'therapeutic' range as described. *Lower daily doses of digitoxin are recommended by the authors to achieve target serum concentrations of 8–18 ng/mL digitoxin. This differs from the recommended daily dose of 0.05–0.3 mg digitoxin for rate control in ESC guidelines for management of AF,[26] which do not recommend certain target serum concentrations for digitoxin. ACE-I: ACE-inhibitor; ARB, angiotensin receptor antagonist; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta blocker; CCB: calcium channel blocker; CRT: cardiac resynchronization therapy; MRA: mineralocorticoid receptor antagonist; GFR: glomerular filtration rate; RR: blood pressure.

Recommendations for use of cardiac glycosides in clinical practice

Cardiac glycosides should only be used with proper clinical indications according to best evidence recommended by current guidelines (ESC) as well as very recently reviewed for the increasing number of patients suffering from HF and/or AF:[12,25–27]

Cardiac glycosides still may be considered in symptomatic HF patients (NYHA II–IV) in sinus rhythm despite treatment with ACE inhibitor (or angiotensin receptor blocker), beta-blocker, and a mineralocorticoid-receptor antagonist to reduce risk of hospitalization (ESC HF guidelines, class IIb recommendation).[25] Cardiac glycosides are recommended (with/without beta-blocker) for rate control of AF in HF patients with an ejection fraction ≤ 40% (ESC AF guidelines, class I recommendation).[26] For patient safety, target serum concentrations should be 0.5–0.9 ng/mL for digoxin and 8–18 ng/mL for digitoxin, which is in the lower part of the so called 'therapeutic' range (*Figure 3*). Furthermore, target serum concentrations should be controlled, especially for digoxin in chronic kidney disease due to its predominant renal excretion, whereas excretion of digitoxin is still sufficient even in advanced chronic kidney disease due to its pronounced entero-hepatic recycling.

Funding

U. B., L. A., A. K., and J. B. are involved in the conduct of the DIGIT-HF Trial (https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-005326-38/DE, 24 November 2016) funded by the Federal Ministry of Education and Research (BMBF), Germany.

Conflicts of interest: none declared.

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