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Individual dosage of digoxin in patients with heart failure

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Summary

Backgroud: After the publication of DIG trial, the therapeutic target of serum digoxin concentration (SDC) for the treatment of heart failure (HF) has been lowered (0.40–1.00 ng/ml). However, the majority of equations to calculate digoxin dosages were developed for higher SDCs. Recently, a new equation was validated in Asian population for low SDCs by Konishi *et al.*, but results in Caucasians are unknown.

Aim: This study was aimed to test the Konishi equation in Caucasians specifically targeting low SDCs. Furthermore, the Konishi equation was compared with other frequently used equations.

Design: This was a prospective, multicenter study.

Methods: Clinically indicated digoxin was given in 40 HF patients. The dosage was calculated with the Konishi equation. The SDC was measured at 1 and 6 months after starting digoxin. Adherence to digoxin was monitored with a specific questionnaire.

Results: After exclusion of patients admitting poor adherence, we found a reasonable correlation between predicted and measured SDC ($r = 0.48$; $P < 0.01$) by the Konishi equation. Excluding patients with poor adherence and relevant worsening of renal function, the measured SDC ($n = 54$ measurements) was within the pre-defined therapeutic range in 95% of the cases. The mean, maximal and minimal measured SDC were 0.69 ± 0.19, 1.00 and 0.32 ng/ml, respectively. The correlation was weaker for the Jelliffe, the Koup and Jusko, and the Bauman equations.

Conclusions: This study supports the clinical validity of the Konishi equation for calculating individual digoxin dosage in Caucasians, targeting SDCs according to current HF guidelines.

Introduction

Despite advances in heart failure (HF) treatment and validation of newer drugs such as β-blockers, ACE-Inhibitors, AT-II antagonists and aldosterone antagonists, digoxin still plays an important role for treatment of HF patients who remain significantly symptomatic.[1] Based on *post hoc* analysis of the DIG trial, the optimal therapeutic level for serum digoxin concentration (SDC) has been lowered substantially as compared to previous recommendations, since even SDCs in the former therapeutic range (i.e. ≥1.2 ng/ml) have been found to increase mortality.[2–4] However, most of the equations to calculate the individual dosage of digoxin were tested for SDCs in the former therapeutic range.[5–7] Konishi *et al*.[8] developed a new equation tested for low SDCs, which was shown to be more accurate as compared to prior equations. However, this equation was tested in Asians, who may have a different pharmacokinetic of digoxin as compared to Caucasians.[9,10] The present study is therefore aimed to test the Konishi equation in Caucasian patients, specifically targeting a range of SDC as recommended by current guidelines for treatment of HF.[1] Additionally, we compared the Konishi equation with some of the most frequently used equations, which were tested for higher SDCs.[5–7] Notably, during the course of the current study, another equation targeting low SDCs has been proposed by Bauman *et al*.[11] Therefore, we also compared the Konishi equation with this equation.

Methods

Study design and patient population

This was a prospective, multicenter study conducted at the University Hospital of Basel and the Regional Hospitals of Locarno and Lugano, Switzerland, between October 2006 and May 2009. Forty patients with symptomatic HF and a clinical indication for digoxin according to the Guidelines of the Task Force for Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology were placed on digoxin.[12] The primary aim of the study was to assess adherence to the medical regime in HF patients based on a specific questionnaire (CARDIA questionnaire), and the measurement of SDC during follow-up. Details of this study have been described previously.[13] The current study is a *post hoc* analysis aimed to test the clinical validity of the Konishi equation to calculate the individual digoxin dosage. Inclusion criteria were symptomatic HF NYHA class ≥2, systolic left ventricular dysfunction (LVEF ≤45%) and age of ≥18 years. Exclusion criteria were mainly related to absolute or relative contraindication to digoxin, including severe renal insufficiency (creatinine clearance ≤30 ml/min, estimated by Cockcroft–Gault), AV-block grade II or III without pacemaker, sinus bradycardia (resting heart rate <50 beats/min.) without pacemaker, hypokalemia (<3.5 mmol/l) or hypercalcemia (>2.64 mmol/l) not correctable with medical treatment, acute coronary syndrome <1 month, hypertrophic cardiomyopathy, pre-excitation syndromes, severe dementia, pregnancy, unwillingness or inability to give informed consent and concomitant use of drugs known to have a relevant pharmacokinetic interaction with digoxin, except for spironolactone, which has been shown to have limited interaction with digoxin.[8] The study complies with the Declaration of Helsinki and was approved by the local ethics committees. All patients gave written informed consent.

Dosage of digoxin and follow-up

The individual dosage of digoxin was calculated as proposed by Konishi *et al*.[8] using the following equation:

$$\text{Daily dosage of digoxin (ug/day)} = \text{SDC (ng/ml)} \times [2.22 \times \text{Ccr (ml/min.)} + 25.7].$$

where SDC is the target SDC and Ccr is the estimated clearance of creatinine as calculated with the Cockcroft–Gault equation.[8,14]

The target SDC ranged between 0.60 and 0.80 ng/ml depending on the renal function and the available dosages of digoxin pills (0.125 and 0.250 mg). The pre-defined therapeutic range of SDC was between 0.40 and 1.00 ng/ml, as recommended by recent guidelines.[1] All patients were instructed to take their digoxin pills regularly between 08:00 and 10:00. All serum digoxin measurements were performed in the early afternoon (between 14:00 and 16:00) in order to measure a steady state concentration. The SDC was determined with enzyme immunoassay [VIDAS® Digoxin, BioMérieux SA, France in the centers of Locarno and Lugano (17 patients), and COBAS®, Roche-Diagnostics, GmbH, Germany in the center of Basel (23 patients)]. After baseline assessment and introduction of digoxin treatment, patients were followed for 6 months with follow-up visits and measurement of the SDC after 1 and 6 months. Detailed medical history, clinical and laboratory examination, including SDC, creatinine levels and electrolytes, were performed at baseline and at follow-up visits. All patients were asked to complete a structured and validated questionnaire about their adherence to medical treatment at each follow-up

visit (CARDIA Questionnaire).[15] The questionnaire consisted of the following question: 'In the past month, how often did you take your medications as the doctor prescribed? (i) all of the time (100%); (ii) nearly all of the time (90%); (iii) most of the time (75%); (iv) about half the time (50%); and finally (v) less than half the time (<50%)'. Poor adherence was defined as a medication intake of ≤75%.

Comparison with prior equations

The Konishi equation, which was used to calculate the individual dosage of digoxin in the current study, was compared with the equations formulated by Jelliffe *et al.*,[5,6] Koup and Jusko *et al.*[7] and the most recently developed equation by Bauman *et al.*[11] (Table 1).

Statistics

Continuous data are presented as mean ± SD or median (interquartile range) as appropriate. Categorical data are presented as numbers and percentages. The correlation between the measured and the predicted SDC by the different equations was tested with a linear regression model and Bland–Altman analysis. The comparison between the measured and the predicted SDC were also tested in terms of the root mean square error. Potential interactions between renal function, and differences between measured and predicted SDC were tested with a linear regression model. Interaction of predicted and measured SDC with other baseline characteristics were tested using the Fisher's test for nominal variables. Continuous variables were tested using the Student's *t*-test or the Mann–Whitney U-test as appropriate. Differences in measured SDC between patients with stable renal function and good adherence, patients with poor adherence and patients with relevant worsening of renal function were evaluated with the Mann–Whitney test. A *P*-value of ≤0.05 was considered statistically significant. Analyses were performed using the commercially available statistical package SPSS version 15.0.

Results

The baseline characteristics of the 40 patients included in the study are shown in Table 2. The median age of the patients was almost 70 years and the mean estimated clearance of creatinine was ∼60 ml/min., indicating a high prevalence of patients with chronic kidney disease. The first follow-up visit after 1 month was performed in all patients. The second follow-up visit was performed in 31 patients: one patient died because of sepsis, six patients withdrew consent and in two patients digoxin was stopped by the general practitioner because of presumed digoxin related side effects (one patient had a symptomatic bradycardia and one patient had minor gastrointestinal side effects). Of note, the SDC was in the therapeutic range in the latter two patients at visit month 1. Thus, 71 measurements of the SDC were performed in these 40 patients.

Digoxin dosage and correlation between the measured and the predicted SDC by the Konishi equation

The daily dosages of digoxin based on the Konishi equation are shown in Table 3.

Overall, 56 out of 71 measured SDC (79%) were within the pre-defined therapeutic range (0.40–1.00 ng/ml). Ten (14%) measured SDC (in eight patients) were within the sub-therapeutic range (<0.40 ng/ml) and five (7%) measured SDC (in five patients) were within the supra-therapeutic range (>1.00 ng/ml). The mean, maximal and minimal measured SDC were 0.69 ± 0.31, 1.70 and 0 ng/ml, respectively.

Table 1 Equations to calculate the dosage of digoxin

Author	Equation
Konishi	SDC (ng/ml) = digoxin dosage (ug/day)/[2.22 × Ccr (ml/min) + 25.7]
Jelliffe[a]	SDC (ng/ml) = −0.416 + (0.185 × TBS)
Koup and Jusko[b]	SDC (ng/ml) = [F × dosage of digoxin (ug/day) × 1000]/[(1.303 × Ccr) + Cnr] × τ
Bauman[c]	SDC (ng/ml) = 1.345 + (0.287 × dose of digoxin) − (0.007 × Ccr) − (0.011 × IBW)

Ccr, estimated creatinine clearance by Cockcroft–Gault for all equations.
[a]TBS =(daily dosage of digoxin/[14+(Ccr/5)]/100)/BW, BW: body weight (both, total BW and ideal BW as calculated by Devine were used as proposed by Jelliffe).
[b]F: bioavailability of oral digoxin (=0.75); Cnr: non-renal clearance of digoxin (=41ml/min); τ: dosing interval (=1440 min/day).
[c]IBW: body weight as calculated by the method of Devine. Dose of digoxin is coded as 1 = 0.0625, 2 = 0.125 and 3 = 0.250 mg/day.

Of note, six patients admitted poor adherence to medical regime with the CARDIA-Questionnaire. Among patients with sub-therapeutic SDC ($n = 8$), five admitted poor adherence (seven of 10 SDC in the sub-therapeutic range). All patients with supra-therapeutic SDC ($n = 5$) experienced a relevant worsening of the renal function during follow-up (five of five SDC in the supra-therapeutic range), defined as a reduction of the estimated creatinine clearance >20%. In none of the patients, the sub-therapeutic SDC could be explained by an improvement in renal function or the concomitant use of drugs with a pharmacokinetic interaction.

Table 2 Baseline characteristics

	Total (n=40)
Male gender, n (%)	33 (83)
Age (years), mean ± SD	69 ± 12
BMI (kg/m^2), mean ± SD	26.8 ± 5.0
Creatinine (μmol/l), mean ± SD	116 ± 38
Estimated creatinine clearance (ml/min), mean ± SD	57 ± 23
Chronic kidney disease	
Stage 2 (%)	10 (25)
Stage 3 (%)	28 (70)
BNP (pg/ml), median/IQR	517 (250–1020)
LVEF (%), mean ± SD	30 ± 7
Systolic blood pressure (mmHg) mean ± SD	122 ± 18
Diastolic blood pressure (mmHg) mean ± SD	71 ± 12
Heart rate (beats pro minute) mean ± SD	72 ± 10
Coronary artery disease (%)	26 (65)
Prior hospitalization for HF (%)	26 (65)
Risk factors	
Diabetes (%)	16 (49)
Hypercholesterolemia (%)	19 (48)
Hypertension (%)	27 (68)
Family history (%)	10 (25)
Smoking (%)	9 (23)
Medication	
Aspirin (%)	20 (50)
β-blockers (%)	36 (90)
ACE-inhibitors (%)	25 (63)
AT-II antagonists (%)	17 (43)
Aldosterone antagonists (%)	25 (63)
Loop diuretics (%)	31 (78)
Oral anticoagulation (%)	20 (50)
Statins (%)	27 (68)

BMI: body mass index (kg/m^2); IQR: interquartile range; Chronic kidney disease Stages 2 and 3, estimated glomerular filtration rate of 60–89 ml/min/1.73 m^2 and 30–59 ml/min/1.73 m^2, respectively; BNP: brain natriuretic peptide; LVEF: left-ventricular ejection fraction; ACE: angiotensin converting enzyme; AT-II: angiotensin II.

After exclusion of SDCs measured in patients admitting poor adherence (six patients, eight SDCs), patients experiencing a relevant worsening of renal function (eight patients, eight SDC) or having both, poor adherence and worsening of renal function (one patient, one SDC) a total of 54 SDC measurements were analyzed, of which 51 (95%) were within the therapeutic, three (5%) within the sub-therapeutic and 0 (0%) within the supra-therapeutic range, respectively. In this cohort the mean, maximal and minimal measured SDC were 0.69 ± 0.19, 1.00 and 0.32 ng/ml, respectively. Differences in measured SDCs among patients with stable renal function and good adherence, patients admitting poor adherence and patients experiencing a relevant worsening of the renal function, are shown in Figure 1. The SDC

Table 3 Digoxin dosage

	Total (n = 40)
Digoxin dosage at baseline (mg/day), mean ± SD	0.105 ± 0.039
Digoxin dosage at baseline (mg/day) (%)	
0.0625[a]	12 (30)
0.089[b]	9 (23)
0.125[c]	15 (37)
0.188[d]	4 (10)

[a]One pill of digoxin 0.125 mg every other day.
[b]One pill of digoxin 0.125 mg 5 day/week.
[c]One pill of digoxin 0.125 mg/day.
[d]One pill of digoxin 0.125 mg/day alternate with two pills of digoxin 0.125/day.

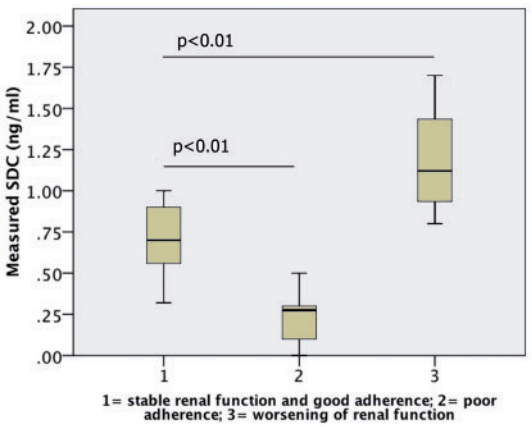

Figure 1. Differences in measured SDC (ng/ml) among patients with good medical adherence and stable renal function (1), patients with poor medical adherence (2) and patients with relevant worsening of renal function (3) during follow-up.

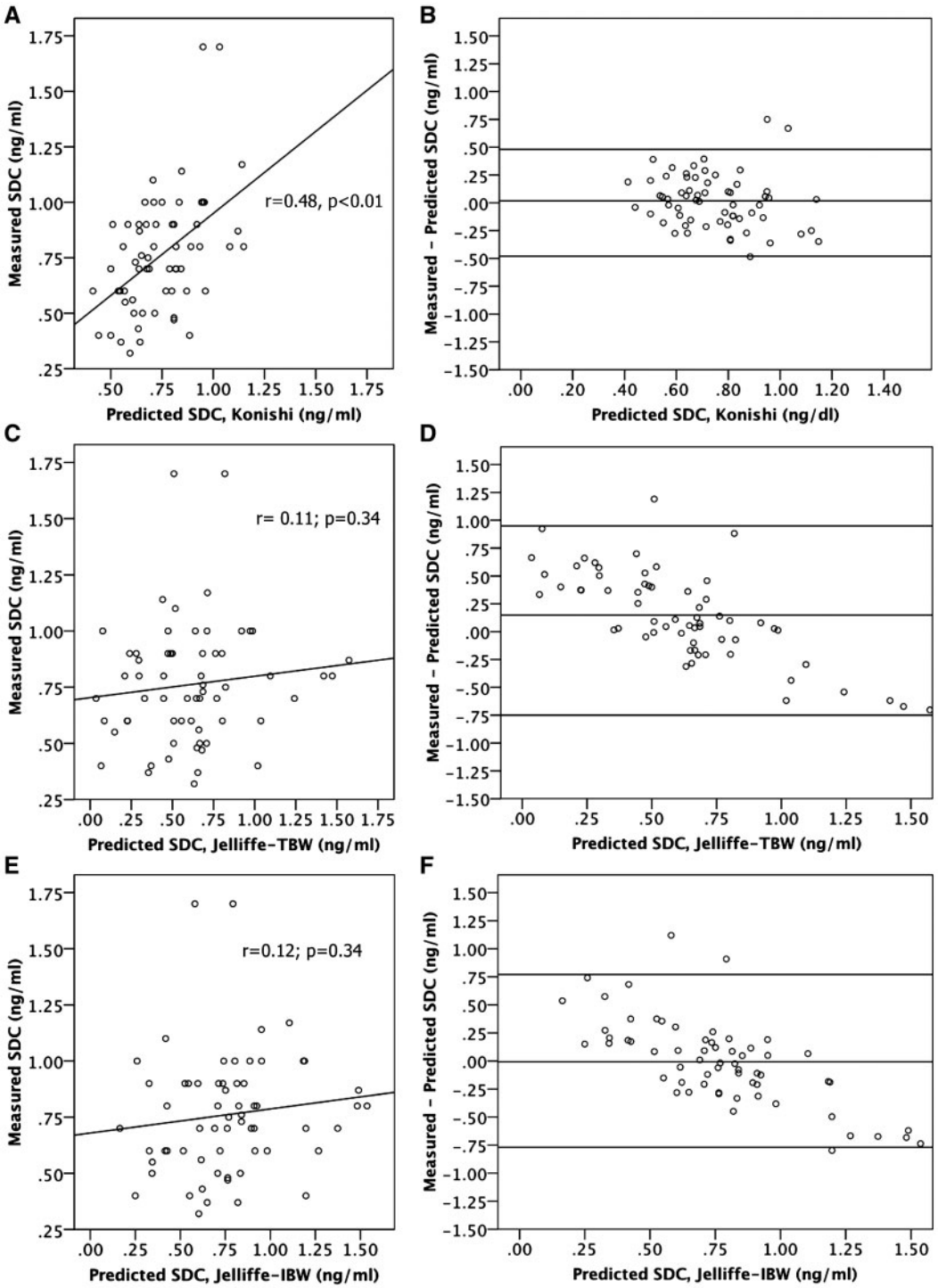

Figure 2. Linear-regression analyses and Bland–Altman analyses showing the correlation between the measured and the predicted SDC (ng/ml) according to the Konishi equation (**A** and **B**), the Jelliffe equation (**C** and **D** for total body weight, and **E** and **F** for ideal body weight), the Koup and Jusko equation (**G** and **H**) and the Bauman equation (**I** and **J**). Note that the Konishi equation shows the best correlation in the linear regression model and less dispersion of the values in the Bland–Altman plot.

was significantly lower in patients admitting poor adherence, and higher in patients with relevant worsening of the renal function as compared to other patients.

In the cohort of patients with good adherence the correlation between the measured and the predicted SDC was reasonable ($r = 0.48$; $P < 0.01$) (Figure 2A and B). Furthermore, there was no

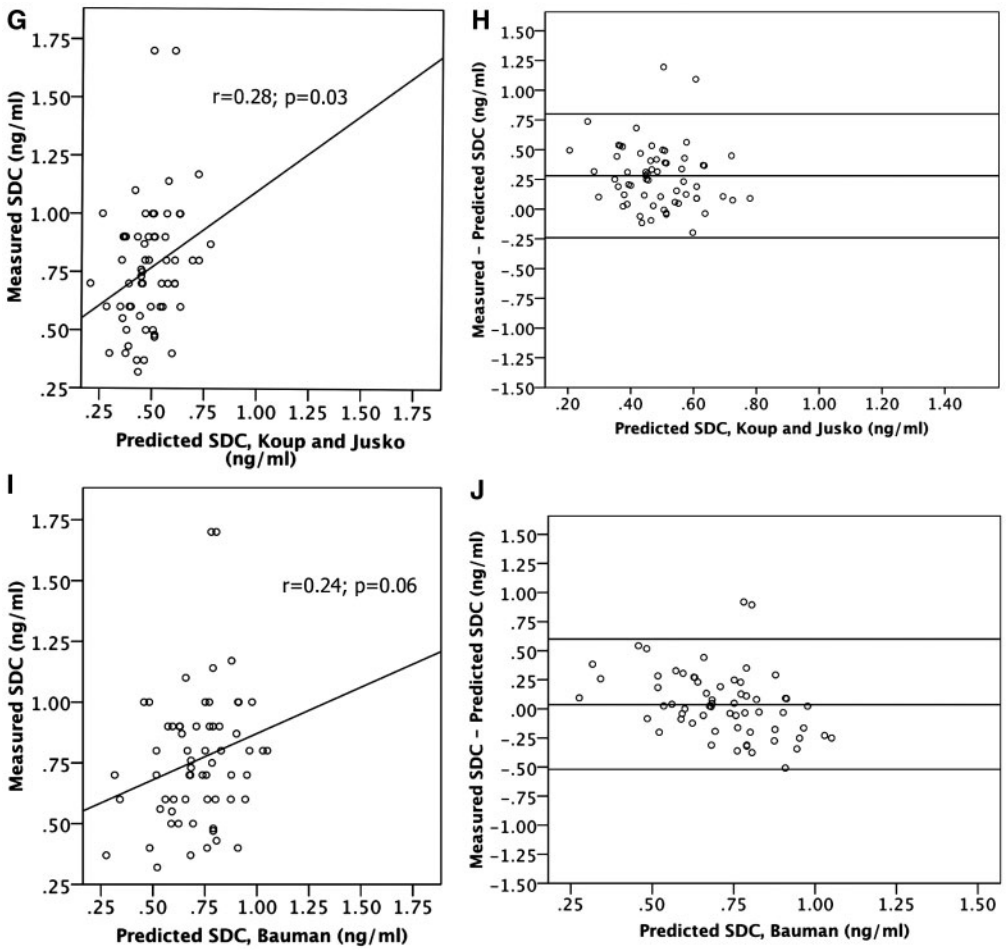

Figure 2. Continued.

relevant interaction between the estimated creatinine clearance and the difference between measured and predicted SDC ($r = 0.06$; $P = 0.62$), suggesting that the validity of the Konishi equation seems to apply for a wide range of renal function, as it was tested in the current study (Figure 3). Of note, the predicted SDC was calculated based on the estimated creatinine clearance at the time of blood sampling for measurement of SDC.

Comparison with other equations

Figure 2 shows the linear-regression analyses and Bland–Altman analyses describing the correlation between the measured and the predicted SDCs for the different tested equations. The Konishi equation showed a stronger correlation ($r = 0.48$; $P < 0.01$) as compared to the other tested equations, including the Jelliffe equation ($r = 0.11$; $P = 0.34$ for total body weight, and $r = 0.12$; $P = 0.34$ for ideal body weight), the Koup and Jusko equation ($r = 0.28$; $P = 0.03$) and the Bauman equation ($r = 0.24$; $P = 0.06$). A comparison between the measured and the predicted SDCs for the different equations were also tested by the root mean square error, which again demonstrated the lowest values, meaning higher accuracy, for the Konishi equation (Table 4).

No interaction of predicted and measured SDC with baseline characteristics could be found. Also, method used to determine SDC and concomitant medication using including spironolactone did not influence results (data not shown).

Discussion

The correlation between the measured SDC and the predicted SDC by the Konishi equation was reasonable in Caucasian patients with HF. In particular, more than 9/10 of the measured SDC were within the therapeutic range of 0.40–1.00 ng/ml in case of good medical adherence and stable renal function. The Konishi equation showed a stronger correlation between the measured and the predicted SDC as

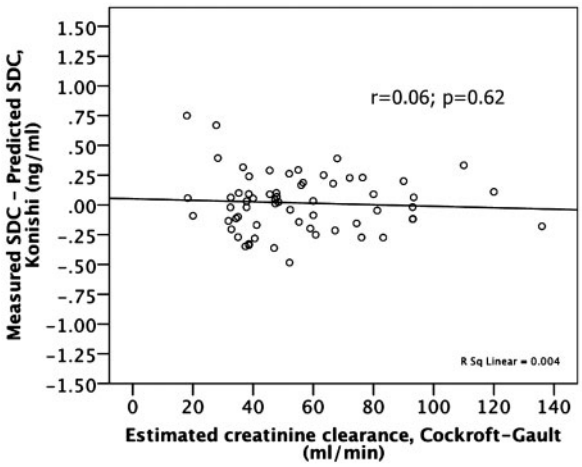

Figure 3. Linear-regression analysis between estimated creatinine clearance (as calculated with the Cockcroft–Gault equation, ml/min), and differences between measured and predicted SDC (ng/ml) to test the interaction of renal function on the performance of the Konishi equation.

Table 4 Estimated root mean square errors (RMSE)

Equation	RMSE, median/Range
Jelliffe–TBW	0.30/0.01–1.19
Jelliffe–IBW	0.20/0.01–1.12
Koup and Jusko	0.25/0.01–1.19
Bauman	0.19/0.00–0.92
Konishi	0.17/0.01–0.75

RMSE, root mean square error; TBW, total body weight; IBW, ideal body weight.

compared to other equations previously validated for higher SDC-targets, but also as compared to the most recent equation by Bauman *et al.*, which was tested for low SDCs in Caucasian patients.

Despite development of more modern drugs, digoxin is still being used in case of persistence of HF symptoms on otherwise optimal medical treatment.[1,16] Thus, even in the modern era, up to 70% of HF patients are treated with digoxin.[17,18] However, since digoxin has a narrow therapeutic range and toxic side-effect are expected in case of over dosage, caution is required when prescribing this drug and choosing the optimal individual dosage is of utmost importance. Based on the results of *post hoc* analyses of the DIG trial, the therapeutic range of SDC for HF has been reviewed and lowered to 0.40–1.00 ng/ml, since patients treated in this range of SDC had better prognosis as compared to patients on placebo, while a SDC between 1.0 and 1.2 ng/ml was neural and >1.2 ng/ml even associated with increased mortality.[1–4,16] However, the majority of equations used for calculation of the individual dosage of digoxin, included the one used in the DIG trial, were developed for higher targets of SDC.[5–7] Recently, Konishi *et al.* [8] developed a new equation in Asian HF patients, which was shown to be more accurate and precise as compared to prior equations, when targeting a low SDC. Since Asians and Caucasians may have different pharmacokinetic of digoxin we aimed to test this equation in a cohort of Caucasian HF patients.[9,10] We specifically targeted SDCs between 0.40 and 1.00 ng/ml as recommended by the recent guidelines for treatment of HF patients.[1]

The results of the current study confirm the superiority of the Konishi equation for predicting SDC as compared to prior equations also in Caucasian HF patients. We also compared the Konishi equation with the Bauman equation, which was recently developed in Caucasians and tested for low SDCs. Notably, the current study suggests a better performance of the Konishi equation as compared with the Bauman equation for predicting SDC. This may reveal a weakness of the Bauman equation, which was developed in a smaller patient cohort, without rigorous control of the medical adherence and, more importantly, without testing the equation in a validation cohort.[11]

By Konishi equation the individual dosage of digoxin is calculated based on the target SDC and the renal function as estimated by Cockcroft–Gault.[8] Therefore, this equation can be easily implemented in clinical care, since age, gender and serum creatinine concentration are the only variables needed for calculating the individual dosage of digoxin.

Comparison with prior study

Jones *et al.* recently tested the equation of Konishi *et al.* for prediction of SDC using 36 blood samples derived from 34 patients treated with digoxin for HF or atrial fibrillation. Though not specifically mentioned, most of the patients were probably Caucasians, since this study was done in Australia. In this population a weaker correlation between the measured and the predicted SDC was found, especially at low SDCs. However, in this study the adherence to the medical regime was not tested, timing of blood sampling was not precisely defined and a large part of patients, especially those with atrial fibrillation, were treated for higher targets of SDC.[19]

Clinical implications

In case of good adherence and stable renal function, >90% of the measured SDCs were within the pre-defined therapeutic range and the maximal measured SDC was 1.00 ng/ml. The numerical correlation between the difference in measured and predicted SDC, and the estimated creatinine clearance was weak and statistically not significant, suggesting that there is no relevant shift towards a worse accuracy of the Konishi equation among patients with impaired renal function. However, some patients with worsening of renal function experienced a significant raise in SDC (see outliers in Figure 2A and B) with a maximal measured SDC of 1.70 ng/ml. Notably, these values were higher than predicted by the Konishi equation even using creatinine values measured at the time of blood sampling for measurement of SDC. This could be a consequence of rapid deterioration of renal function, non-steady-state conditions of serum creatinine concentration and, as a consequence, an overestimation of the creatinine clearance by the Corckcrof–Gault equation. Therefore, considering that chronic kidney disease is a frequent comorbidity in patients with HF and renal function may rapidly change, regular controls of renal function and SDCs are very important in such patients.

A recent work by Vaz Pérez *et al.*[20] suggested that digoxin therapy may negatively influence medium- and long-term mortality in patients hospitalized for acute HF. The association between use of digoxin and outcome was independent from use of diuretics and serum creatinine, but not independent from other clinical factors. Therefore, this association may be related to sicker patients being more often treated by digoxin. Still, overdosage of digoxin in some patients might be another reason. SDCs during initial hospitalization and long-term follow-up were unknown, but worsening of renal function is particularly frequent in patients with acute HF,[21,22] underscoring the importance of monitoring of renal function in such patients.

Possibly, the Konishi equation may be used to further adapt digoxin dose in case of changes in renal function, but prospective studies are required to test this. Still, the Konishi equation may be a useful and simple tool helping physicians to find the optimal individual dosage when starting digoxin.

As shown in Table 3, dosing of digoxin with the available pills (0.125 and 0.250 mg) may be complex. This is particularly true for patients with reduced or nearly preserved renal function, where digoxin dosing changes every second day are necessary. This may negatively influence adherence to the medical therapy, which in turn is known to affect prognosis of HF patients.[23] In this context, an effort towards production of digoxin pills with specific dosages to target 'lower' SDCs should be undertaken by the pharmaceutical companies, in order to simplify digoxin dosing in the daily practice.

Limitations

The small number of patients is a limitation of this study. Even though patients taking drugs known to interfere relevantly with the pharmacokinetic of digoxin were excluded and adherence to digoxin was monitored with a specific questionnaire, variation in the measured SDC due to these reasons cannot be completely excluded.

Patients with severe renal function were excluded and patients with normal renal function were underrepresented in the studied population, limiting the applicability of these results to such patients.

The results of this study are applicable to digoxin only, since digitoxin has different pharmakokinetic profiles as compared to digoxin. Therefore, we cannot provide options to calculate SDC in patients taking digitoxin based on the data of the current study. Digoxin is, however, the only cardiac glycosid that has been evaluated in placebo-controlled trials, and represents therefore the preferred cardiac glycosid for HF treatment according to the most recent guidelines.[1,2]

Just the Konishi equation has been used to calculate the individual dosage of digoxin; the other formulas might have indicated different dosages to reach the same target concentration. Thus, it cannot be excluded that these differences could have an influence on the compared correlations.

Finally, this study did not test the effects of using this or other equations to predict SDC on outcome. Further studies should investigate if safety and efficacy may be improved by doing so and which equation may be best suited.

Conclusion

The results of this study support the clinical validity and the superiority of the Konishi equation as compared to other frequently used equations for the calculation of the individual dosage of digoxin even in Caucasian patients with HF. However, regular control of renal function is recommended to avoid overdosage of digoxin, particularly when cardiac and renal conditions are not stable.

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