Published in final edited form as:

Pharmacotherapy. 2014 November ; 34(11): 1121–1131. doi:10.1002/phar.1480.

Use of a Simplified Nomogram to Individualize Digoxin Dosing versus Standard Dosing Practices in Patients with Heart Failure

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Abstract

Study Objectives—To compare the frequency of achieving a therapeutic serum digoxin concentration (SDC), defined as 0.5–0.9 ng/ml, by using a simplified nomogram to individualize digoxin dosing with standard dosing practices in patients with heart failure, and to characterize the relationship between genetic polymorphisms of the *ABCB1* gene and SDC.

Design—Prospective study with a historical control group.

Setting—Outpatient care center of an urban academic medical center.

Patients—One hundred thirty-one adults with heart failure due to left ventricular dysfunction who were treated with digoxin.

Intervention—Digoxin doses were determined either by the dosing nomogram (65 patients) or standard care (SC; 66 patients) by using a historical controls who were randomly selected from a list of SDCs obtained from laboratory records and who had their digoxin doses determined by standard dosing practices.

Measurements and Main Results—The primary end point was the proportion of patients achieving a steady-state SDC of 0.5–0.9 ng/ml; secondary end points were mean SDC and proportion of patients achieving a steady-state SDC < 1.0 ng/ml. Postdistributive steady-state SDCs were measured 2–4 weeks after digoxin dosage adjustment or initiation. Therapeutic SDCs were achieved with similar frequency in both groups (38.7% in the nomogram group vs. 34.5% in the SC group, $p=0.65$); however, more patients in the nomogram group had SDCs < 1.0 ng/ml than in the SC group (85.0% vs. 44.9%, $p<0.001$). Mean daily digoxin doses were lower in nomogram group (149 ± 67 mcg vs. 177 ± 74 mcg, $p=0.02$), resulting in lower mean SDCs compared with those in the SC group (0.52 ± 0.30 ng/ml vs. 1.12 ± 0.58 ng/ml, $p<0.001$). Patients in the pharmacogenetic substudy provided blood samples for genotyping of three common *ABCB1*

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Dr. Bauman served as a consultant to Covis Pharmaceutical.

ClinicalTrials.gov identifier: NCT01005602.

This study was presented at the ACCP Annual Meeting, Austin, Texas, October 17–20, 2010.

single nucleotide polymorphisms: C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642). SDCs were not significantly associated with *ABCB1* genotypes.

Conclusion—Our simplified digoxin dosing nomogram resulted in lower SDCs compared with standard dosing practices but achieved therapeutic SDCs with similar frequency. A greater proportion of patients dosed according to our nomogram had SDCs < 1.0 ng/ml, consistent with consensus guidelines. Genetic polymorphisms of the *ABCB1* gene were not associated with SDC.

Keywords

digoxin; heart failure; dosing nomogram

Digoxin is a digitalis glycoside that is associated with both symptomatic improvement and fewer hospitalizations in patients with heart failure.¹⁻³ In the Digitalis Investigation Group (DIG) trial, digoxin had no effect on mortality (primary endpoint) but was associated with fewer hospitalizations and the composite of death or hospitalization for worsening heart failure compared with placebo in patients with heart failure due to left ventricular dysfunction.¹ Consequently, consensus guidelines recommend that digoxin be considered as an adjunct to standard therapy in patients with symptomatic heart failure with reduced ejection fraction (HFrEF).⁴⁻⁶

In the last decade, the appropriate target serum digoxin concentration (SDC) for the treatment of heart failure has been redefined. Analyses of previous digoxin studies indicate that the target SDC is even narrower than the historical range of 0.8–2.0 ng/ml. An analysis of two digoxin withdrawal studies found that the risk of worsening heart failure was significantly lower in patients treated with digoxin but did not differ across a range of SDCs.⁷ In contrast, several post hoc analyses of the DIG trial found that lower SDCs (e.g., 0.5–0.9 ng/ml) were associated with lower mortality and hospitalization rates compared with placebo whereas higher SDCs offered no additional benefit or increased the risk of these adverse outcomes compared with placebo.⁸⁻¹⁰ In response to these findings, consensus guidelines from the Heart Failure Society of America (HFSA) and the American College of Cardiology Foundation/American Heart Association suggest dosing digoxin to achieve a target SDC of < 1.0 ng/ml or between 0.5–0.9 ng/ml.^{4, 6}

Although target SDCs have been lowered for patients with heart failure, digoxin dosing methods had not been modified to address these new recommendations until recently. To address the need for modern digoxin dosing methods, members of our study group developed a simplified dosing nomogram (University of Illinois at Chicago [UIC] nomogram) that targets the modern therapeutic SDC range (specifically 0.7 ng/ml).¹¹ A retrospective analysis was conducted of 54 patients treated with digoxin, the majority of whom had HFrEF, for whom steady-state SDC had been attained. Linear regression analyses were performed relating clinical factors known to affect digoxin dosing (weight, renal function) to SDC. An algorithm that targeted a SDC target of 0.7 ng/ml was then developed as a function of both ideal body weight (IBW)¹² and creatinine clearance (Cl_{cr}),¹³ with the latter calculated by using IBW (Figure 1). When compared with two historical dosing methods,¹⁴⁻¹⁸ the UIC nomogram performed similar to, or better, than these traditional dosing methods in terms of predicting SDC. Additionally, the UIC nomogram offers the

convenience of simplicity, as minimal calculations are required, and real-time application for clinicians.

Digoxin is a well-known substrate for the membrane transporter, P-glycoprotein (P-gp), which plays an important role in the pharmacokinetics of digoxin and is a target for drug-drug interactions leading to elevated SDC. The *ABCB1* gene encodes for P-gp and several single nucleoside polymorphisms (SNPs), including C1236T, G2677T, and C3435T, and associated haplotypes within this gene have been linked to altered P-gp expression.¹⁹⁻²⁸ Although some studies have associated genetic variations in one or more of these SNPs and/or associated haplotypes with altered digoxin pharmacokinetic parameters, others have failed to demonstrate significant associations.²⁹⁻³³ Therefore, whether genetic polymorphisms of the *ABCB1* gene influence digoxin dosing and may serve as targets for genetically tailored dosing of digoxin remain unknown.

Our study was designed to compare the proportion of patients with heart failure treated with digoxin achieving the contemporary therapeutic SDC by using the UIC nomogram with standard dosing practices. We also sought to characterize the relationship between genetic variability in the *ABCB1* gene and digoxin dosing.

Methods

Study Design, Setting, and Patient Selection

Study participants were treated at the University of Illinois Hospital and Health Sciences System (UI Health; Chicago IL). The study consisted of a prospective study group, for whom the digoxin dose was determined by the UIC nomogram¹¹ (nomogram group), and a historical control group, for whom the digoxin dose was determined by standard dosing practices (standard care [SC] group). Patients aged 21 years or older with HFrEF and either treated chronically with digoxin or being initiated on digoxin therapy at study entry (nomogram group) were eligible for participation. For inclusion in the SC group, patients were required to have had at least one documented steady-state SDC, defined as a postdistribution SDC (> 6 hours after the last dose, with the administration time assumed to have occurred between 7 and 9 A.M. unless otherwise documented) measured 2–4 weeks after digoxin initiation or dosage adjustment. Patients were excluded if they were pregnant; had unstable renal function at baseline, defined as either a rise in serum creatinine concentration by 0.5 mg/dl or a decrease in Cl_{Cr} by 25% or more within 2–4 weeks of study entry; had stage 5 kidney disease requiring renal replacement therapy; or were taking drugs known to interact with digoxin (amiodarone, quinidine, verapamil, or macrolide antibiotics). Patients in the nomogram group were identified from the investigators' clinical practice in the UI Health Heart Center (cardiology clinic) between January 2007 and July 2008; they provided written informed consent before participating. Subjects who provided informed consent to the study were also asked to provide informed consent to the pharmacogenetic substudy. Subjects in the SC group were randomly selected from a list of SDCs obtained from the UI Health laboratory records between January 2003–August 2006 provided that inclusion and exclusion criteria were met. This study was approved by the UI Health Institutional Review Board.

Interventions and Assessments

Patients in the nomogram group had their doses of digoxin determined from the dosing nomogram based on their IBW and Cl_{Cr} at baseline (Figure 1). In digoxin-naïve patients, digoxin doses were started at the dose derived from the nomogram, and a postdistribution steady-state SDC was measured 2–4 weeks after study entry as well as a serum creatinine concentration to assess for any changes in renal function from baseline. For patients taking chronic digoxin therapy at the time of enrollment, if a digoxin dosage adjustment was necessary, the new dose was prescribed, and a postdistribution steady-state SDC was measured 2–4 weeks later. For patients taking chronic digoxin therapy who did not require a dosage adjustment, steady-state was confirmed (≥ 2 weeks of therapy), and a postdistribution SDC was measured as described above. At the time steady-state SDCs were measured, medication adherence (self-reported) was assessed, and a blood sample for the pharmacogenetic analyses was collected from patients who consented to the pharmacogenetic substudy. For patients in the SC group, the SDC that best represented steady-state SDC (described in the inclusion criteria) and serum creatinine concentration obtained within 2–4 weeks of study inclusion were used for data analysis. For all patients, the following data were collected: demographic information, height, weight, renal function, medical history, and concomitant medications.

For patients in the nomogram group, measurement of SDC was performed by the UIC College of Pharmacy Clinical Research Laboratory (CRL) by using a competitive enzyme immunoassay method (Digoxin [DIG] Test System Accu Bind ELISA; Monobind, Inc., Lake Forest, CA). For patients in the SC group, SDCs were measured as part of routine care and performed by the UI Health Clinical Pathology Laboratory by using a turbidimetric inhibition immunoassay method using digoxin-specific antibodies (Synchron LX; Beckman Coulter, Fullerton, CA). The cross-reactivity of both assays to spironolactone is negligible; therefore, patients treated concomitantly with spironolactone were not excluded. Both assay methodologies have been shown to produce comparable results.³⁴ Steady-state creatinine assays in the nomogram group were performed by the CRL by using a commercially available kit (Creatinine [Direct] Procedure, CHEM-TROL normal, CHEM-TROL Elevated; Eagle Diagnostics, DeSoto, TX).

Pharmacogenetic analyses were performed by the UIC College of Pharmacy Pharmacogenomics Laboratory. Genomic DNA was isolated from ethylenediaminetetraacetic acid–treated whole blood using the Gentra Puregene extraction kit (Qiagen, Inc., Valencia, CA), quantified, and quality checked with Picogreen (Invitrogen, Eugene, OR) and Nanodrop (Thermo Scientific, Wilmington, DE) assays. Genotyping for C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642) SNPs was performed by using Pyrosequencing Technology (Qiagen, Inc.) and a previously described and validated assay.³⁵ Genotype calls were made blind to the clinical status of participants, and the genotype call rate was 100% for those who provided DNA for study.

Statistical Analysis

The primary endpoint for this study was the proportion of patients achieving a steady-state SDC ranging from 0.5–0.9 ng/ml. Assuming a 61% baseline rate of achieving the desired

SDC based on previous data¹¹, a sample size of 130 subjects (65 in each group) was estimated to demonstrate a 25% (clinically significant) increase in the number of subjects achieving the desired SDC with 80% power and a two-sided alpha of 0.05. Secondary endpoints included mean SDC and proportion of patients achieving a steady-state SDC < 1.0 ng/ml.

Descriptive statistics were used to characterize the study population. Normally distributed continuous data were compared by using unpaired t-tests and analysis of variance. Continuous data that were nonnormally distributed were compared by using Mann-Whitney U and Kruskal Wallis tests. The χ^2 or Fisher exact test was used to compare categorical data. Logistic regression models were used to compare the proportion of patients achieving a steady-state SDC ranging from 0.5–0.9 ng/ml (primary endpoint) between groups. Covariates in these models included demographic variables (age, sex, race-ethnicity) and patient characteristics related to SDC in prior studies (IBW, Cl_{Cr}). Covariates were included in the regression models to increase statistical power and precision given our relatively small sample size, to account for chance differences in covariates between groups and to include observed covariates that are theoretically related to SDC. Models were run without covariates and similar results were obtained. P values were estimated using the bootstrap method.³⁶

Linear regression was used to examine the association between the groups and SDC prediction error defined by the actual SDC of 0.7 ng/ml (the target SDC of the nomogram). Allele and genotype frequencies and the Hardy-Weinberg Equilibrium (HWE) were assessed with Haploview version 4.2 software³⁷. Multiple linear regression permitted tests of association between *ABCB1* SNPs and SDC while holding digoxin dose, body mass index (BMI), and Cl_{Cr} constant as these are related to SDC.¹¹ Models were also adjusted for race-ethnicity, as the *ABCB1* allele frequencies have differed across racial-ethnic groups in some studies (<http://www.ncbi.nlm.nih.gov/SNP/>). Dominant, additive, and recessive effects models were all used to test the association of *ABCB1* SNPs and SDC. An F test was used to compare nested models, one with clinical variables only (BMI, digoxin dose, and Cl_{Cr}) and another with clinical variables plus the three *ABCB1* SNPs. All analyses were performed with two-sided alpha values of $p < 0.05$ considered significant. All statistical analyses were performed with the SAS software package, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

A total of 132 patients were enrolled in the study (66 patients in each study group). One patient in the nomogram group was inadvertently enrolled twice; thus, the second entry was excluded. This resulted in 131 patients (66 in the SC group and 65 in the nomogram group). Baseline characteristics are shown in Table 1; demographic comparisons were similar between groups. The mean $\pm$ SD age of all study participants was 60 ± 15 years and 52% were male; most were of African-American (66%) heritage, which is consistent with the demographic served by UI Health. Significant differences were noted in both baseline renal function and various measures of body habitus. Patients in the nomogram group had a significantly higher IBW and total body weight (TBW) and a trend noted toward higher

BMI. Renal function, as measured by both Cl_{Cr} and estimated glomerular filtration rate (eGFR), was significantly better in patients in the nomogram group. More patients in the nomogram group were treated with evidence-based heart failure therapies compared with the SC group. With the exception of diltiazem, which was prescribed to five patients (four in the SC group and one in the nomogram group), no patients were treated with known inhibitors or inducers of P-gp.

Digoxin Dosing and Steady-State Serum Digoxin Concentration

Table 2 depicts the proportion of patients treated with the various daily digoxin doses within each group. Only 19 (28.8%) patients in the SC group received a digoxin dose consistent with our dosing nomogram. Overall, the mean daily digoxin dose was significantly lower in the nomogram group compared to the SC group (149 ± 67 mcg vs. 177 ± 74 mcg, $p=0.02$). The lower digoxin doses used in the nomogram group resulted in steady-state SDCs that were significantly lower than those achieved in the SC group (0.52 ± 0.30 ng/ml vs. 1.12 ± 0.58 ng/ml, $p<0.001$). The distribution of SDCs for both groups is shown in Figure 2. In the 19 patients in the SC group treated with a digoxin dose consistent with our dosing nomogram, the mean steady-state SDC was 0.86 ± 0.42 ng/ml.

After adjusting for differences between study groups, a similar proportion of patients in both groups achieved the targeted SDC range of 0.5–0.9 ng/ml (34.5% vs. 38.7% in the SC and nomogram groups, respectively, $p=0.65$). However, a greater proportion of patients in the nomogram group achieved the secondary target SDC of < 1.0 ng/ml compared with those in the SC group (85.0% vs. 44.9%, $p<0.001$). Thus, for patients falling outside of the targeted SDC of 0.5–0.9 ng/ml, the nomogram group was more likely to be below this target, whereas SDCs exceeded 1.0 ng/ml in more than half of the SC group (Figure 3). Of the 19 SC patients who received digoxin doses consistent with our dosing nomogram, 9 (47.4%) patients achieved the target SDC of 0.5–0.9 ng/ml, and 12 (63.2%) had SDCs < 1.0 ng/ml.

Ten (15.4%) patients in the nomogram group were noted to have a significant change in renal function (increase or decrease in steady-state creatinine concentration > 0.5 mg/dl). The SDCs in these patients ranged from 0.2–1.0 ng/ml; seven had SDCs within the desired range of 0.5–0.9 ng/ml. Only one (8.3%) of the 12 patients in the nomogram group characterized as morbidly obese ($BMI \geq 40$ kg/m²) had SDCs within the desired range of 0.5–0.9 ng/ml; the remainder fell below this range (0.37 ± 0.24 ng/ml).

Differences in SDC prediction errors between the nomogram and SC groups derived from linear regression models are shown in Table 3. Model 1 shows that patients in the nomogram group had a lower prediction error compared with those in the SC group (-0.41 ng/ml, $p<0.0001$ adjusted for digoxin dose, renal function, BMI, age, and sex at baseline). Model 2 allows the association of the nomogram with SDC prediction error to vary across two strata of renal function ($Cl_{Cr} < 50$ ml/min and $Cl_{Cr} \geq 50$ ml/min). In patients with a $Cl_{Cr} < 50$ ml/min, the prediction error was -0.62 ng/ml lower in the nomogram group compared to the SC group. However, in patients with a $Cl_{Cr} \geq 50$ ml/min, the difference in SDC prediction error between groups was lower (-0.26 ng/ml). The product term (nomogram group $\times$ renal function) was statistically significant ($p=0.026$), suggesting that the UIC

nomogram is more precise in patients with renal impairment compared to SC, but precision is diminished as renal function improves.

Pharmacogenetic Substudy

The pharmacogenetic substudy consisted of 55 patients. The allele frequencies of the *ABCB1* variants are shown in Table 4 along with the corresponding SDCs for each genotype. Variant alleles were observed at C1236T, C3435T, and G2677T/A with frequencies of 0.436, 0.509, and 0.309, respectively, with the most common being a single allele at C3435T (0.455). There were no deviations from the Hardy-Weinberg Equilibrium identified for any of the SNPs examined. No significant differences were observed in SDCs among the various genotypes for each SNP. Twelve (21.8%) patients carried the CT/CT/GT genotype combination whereas 2 (3.6%) possessed the TT/TT/TT genotype combination. The mean $\pm$ SD SDCs observed in these variant haplotypes were 0.54 ± 0.40 ng/ml (CT/CT/GT) and 0.48 ± 0.08 ng/ml (TT/TT/TT) compared to those without variant alleles at each SNP: 0.53 ± 0.28 ng/ml ($p=0.91$) and 0.54 ± 0.31 ng/ml ($p=0.81$), respectively. Table 5 demonstrates that the three *ABCB1* variants examined did not significantly explain more variance in SDC than a reduced model containing only clinical variables.

Discussion

Our study provides evidence validating that the UIC nomogram for digoxin dosing successfully achieves SDCs recommended by consensus guidelines for patients with heart failure due to left ventricular systolic dysfunction. The proportion of patients achieving the more narrow range of 0.5–0.9 ng/ml⁶ (primary endpoint) was similar between groups, but the UIC nomogram resulted in nearly 90% of patients achieving the broader SDC range (< 1.0 ng/ml⁴) compared to less than 50% of patients receiving traditional doses of digoxin. This has clinical importance because data suggest that achieving SDCs ≥ 1.0 ng/ml offers no clinical benefit to patients with heart failure compared to lower SDCs and may increase the risk of death and hospitalization compared to placebo.^{7–10} In our study, 31 (47.7%) patients in the nomogram group had SDCs < 0.5 ng/ml, most of whom were clustered near this threshold (~ 0.3 – 0.4 ng/ml [Figure 2]). Although SDCs ≥ 1.0 ng/ml may result in worse outcomes, the clinical benefit of SDCs < 0.5 ng/ml are not known because the lower limit of digoxin's therapeutic range in patients with HFrEF has not been defined. The lower limit of detection of the digoxin assay used in the DIG trial was 0.5 ng/ml.⁸ Thus, the lower threshold of SDC from the post hoc analyses of the DIG trial^{8, 10, 38} was established due to assay limitations, not because of clinical outcomes. In fact, the post hoc analysis by Adams et al implies that SDCs < 0.5 ng/ml may have continued benefit.⁸ For these reasons, we believe it is logical at this point to simply use < 1.0 ng/ml as a therapeutic endpoint for digoxin therapy in heart failure.⁴

To our knowledge, one other modern dosing method for digoxin has been developed and compared to previous dosing strategies. Konishi et al examined the predictability of SDC as a function of six different methods for determining Cl_{Cr} in 181 hospitalized patients.³⁹ They found that measured Cl_{Cr} correlated best with estimated Cl_{Cr} determined by the Cockcroft-Gault method¹³ and proposed a simplified dosing equation for digoxin based on desired

SDC and Cl_{Cr} .³⁹ The Konishi dosing method was subsequently validated in 40 patients with heart failure by Muzzarelli et al.⁴⁰ Using a wider target SDC (0.4–1.0 ng/ml) than we used, 79% of 71 measured SDCs were within the desired range, and 93% of SDCs were < 1.0 ng/ml.⁴⁰ This method was found to be superior to other dosing methods, including the UIC nomogram, in predicting SDC.⁴⁰ If we used the target SDC used by Muzzarelli et al in the present study, 41 (63.1%) patients would have achieved this goal range. Most patients achieved SDCs < 1.0 ng/ml with each method. Thus, both dosing methods are simple and appear comparable, whereas, to our knowledge, the UIC nomogram is the only method that offers the convenience of Web-based and mobile-based applications to aid clinicians.

Given that the overall prediction error was lower using the UIC nomogram compared to SC, the UIC nomogram offers greater precision in digoxin dosing compared to standard dosing practices in patients with heart failure. Dosing precision with the UIC nomogram was greatest (less prediction error compared to SC) in patients with renal impairment. Nearly half of patients with chronic heart failure and more than 60% of patients with acute decompensated heart failure have at least moderately impaired renal function (estimated glomerular filtration rate < 60 ml/min/1.73 m²).^{41, 42} Because renal impairment is common among patients with heart failure, the use of more precise digoxin dosing strategies, such as the UIC nomogram, may optimize digoxin dosing and improve outcomes in patients with heart failure and renal dysfunction.

It is not clear why the UIC nomogram was less precise in patients with heart failure and relatively preserved renal function. In obese patients, estimation of Cl_{Cr} is affected by the weight used in these calculations, potentially impacting dosage adjustments of renally cleared drugs like digoxin.^{43, 44} The UIC nomogram uses IBW (Devine equation¹²) to estimate Cl_{Cr} .¹¹ Because more patients in the nomogram group were overweight or obese (BMI ≥ 25 kg/m²) compared to those on the SC group, we may have underestimated Cl_{Cr} in these patients, resulting in less dosing precision and more SDCs < 0.5 ng/ml. The use of alternative weight inputs in patients with a BMI ≥ 25 kg/m² more accurately estimate Cl_{Cr} using the Cockcroft-Gault method.^{13, 43, 44} Although there remains debate regarding the preferred method for estimating Cl_{Cr} in overweight or obese patients, Winter et al found that a Cl_{Cr} calculation using an adjusted body weight (adjusted body weight = IBW + 0.4[TBW – IBW]) was the least biased and most accurate method in this population.⁴⁴ Using this method, Cl_{Cr} estimates in patients with a BMI ≥ 25 kg/m² were approximately 25% higher compared to our original Cl_{Cr} calculations using IBW (55 ± 23 ml/min vs. 69 ± 32 ml/min in the SC group; 67 ± 25 ml/min vs. 85 ± 40 ml/min in the nomogram group). As a result of this recalculation, dosage increases would have been warranted in 8 patients (12.3%) in the nomogram group (mean BMI 41.6 kg/m²), six of whom had SDCs < 0.5 ng/ml.

SDCs were similar across all genotypes tested in our population. Thus, our findings are consistent with other investigations that found no association between genetic polymorphisms of the *ABCB1* gene and SDC.^{30, 32} Genetic polymorphisms of the *ABCB1* gene have been associated with alterations in digoxin pharmacokinetics.^{29, 31, 33} The reasons for these discrepancies are unknown, but our data did not indicate that incorporating *ABCB1* genotypes improved our dose prediction model for digoxin.

Limitations

The results of our study must be interpreted in the context of its limitations. First, we used a historical control group. As a result, data collection was dependent on the accuracy of medical record documentation, and we may not have been privy to undocumented factors that may have influenced digoxin dosing for patients in the SC group. Additionally, control subjects were treated during an earlier time period than patients in the nomogram group. Second, we did not formally assess adherence or timing of digoxin dose relative to the measurement of SDC. For the SC group, we were dependent on chart documentation for this information, and we attempted to select the SDC that we felt best represented postdistribution steady-state levels (unless otherwise documented, we assumed digoxin administration occurred between 7 and 9 am). We used patient self-report for both adherence and timing of medication administration in the nomogram group. Although poor adherence and timing of digoxin administration may have influenced our results, the SDCs observed in the SC group were similar to those observed in our previous study.¹¹ Further, the differences in digoxin dose and SDC between groups are consistent with the different dosing strategies employed. Thus, we are reasonably confident that alterations in adherence, timing of administration, or both did not significantly affect our results. Third, although different SDC assays were used for the two study groups (one by the medical center laboratory and one in the CRL), both assay methodologies have been shown to yield comparable results.³⁴ Finally, we excluded patients from the study with stage 5 kidney disease requiring renal replacement therapy as well as those with notable drug-drug interactions. Therefore, use of our nomogram cannot be recommended in these patients.

Conclusion

Although the use of our digoxin dosing nomogram was comparable to SC in achieving a target SDC of 0.5–0.9 ng/ml in patients with heart failure, it was superior to SC in achieving the broader target SDC of < 1.0 ng/ml endorsed by the HFSA. Since nearly half of the patients in the nomogram group had SDCs < 0.5 ng/ml, more research is needed to determine the lower limit of digoxin's therapeutic effect. The nomogram offers convenience, ease-of-use, and is also available in both Web- and mobile-based applications for real-time use by clinicians. We did not find any association between genetic polymorphisms of the *ABCB1* gene and SDC.

Acknowledgments

We would like to thank Thomas Stamos, M.D., for allowing us to recruit patients from his clinic. Likewise, we thank Marlos Viana, Ph.D., for providing input on the study design. Finally, we acknowledge the work of Sean P. Kane, Pharm.D., who developed Web-based (clincalc.com/Digoxin/) and mobile-based applications of our digoxin dosing nomogram on Android-enabled (<https://play.google.com/store/apps/details?id=com.clincalc.digoxin&hl=en>) and iOS (<https://itunes.apple.com/us/app/digoxin-calculator/id483020061?mt=8>) mobile devices.

This study was supported by the 2008 American College of Clinical Pharmacy (ACCP) Research Institute Investigator Development Award. Dr. Bishop is supported by a grant from the National Institute of Mental Health (K08MH083888).

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Figure 1.

UIC nomogram for digoxin dosing in patients with heart failure. To select an appropriate digoxin dose, plot a patient's creatinine clearance^a (x-axis) (to convert creatinine clearance to ml/sec, multiply by 0.01667) and ideal body weight^b (y-axis). The point at which these lines intersect is the recommended digoxin dose. If ideal body weight has not or cannot be calculated, an appropriate digoxin maintenance dose can be determined by plotting a patient's creatinine clearance (x-axis) and height (z-axis), depending on the patient's sex. In the digoxin 0.25 mg daily area of the nomogram, one may also consider a digoxin maintenance dose of 0.125 mg every other day alternating with 0.25 mg every other day (average daily dose of 0.1875 mg/day) as represented by the gradual shading of this area.

^a Calculated by using the Cockcroft and Gault equation,¹³ using ideal body weight.

^b Calculated by using the Devine equation.¹²

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Figure 2. Histogram of steady-state serum digoxin concentrations by study group. Horizontal bars (x-axis) represent the percentage of the respective study group for each category of serum digoxin concentrations (bins). Dashed lines represent the target serum digoxin concentration of 0.5–0.9 ng/ml.

Figure 3.
Steady-state serum digoxin concentration ranges by study group.

Table 1

Baseline Demographic and Clinical Characteristics of the Study Patients

Characteristic	Standard Care Group (n=66)	Nomogram Group (n=65)	p Value
Age (yrs)	63 ± 15	58 ± 15	0.064
Male sex	30 (44.1%)	38 (55.9%)	0.136
Race-ethnicity			0.301
African-American	40 (60.6)	46 (70.8)	
Hispanic	10 (15.2)	10 (15.4)	
White	15 (22.7)	7 (10.8)	
Other	1 (1.5)	2 (3.1)	
Anthropometrics			
Ideal body weight (kg) ^a	62 ± 11	67 ± 10	0.02
Total body weight (kg)	85 ± 27	100 ± 34	0.006
Body mass index (kg/m ²)	29.9 ± 8.9	33.2 ± 10.4	0.05
Body mass index ≥ 25 kg/m ²	43 (65.2)	54 (83.1)	0.03
Renal function			
Creatinine clearance (ml/min) ^b	51 ± 22	66 ± 10	<0.001
eGFR (ml/min/1.73 m ²) ^c	59 ± 23	71 ± 22	0.006
Chronic kidney disease stage ^d			0.05
Stage I or II (eGFR ≥ 60 ml/min/1.73 m ²)	33 (50.0)	44 (67.7)	
Stage III (eGFR 30 – 59 ml/min/1.73 m ²)	25 (37.9)	19 (29.2)	
Stage IV or V (eGFR < 30 ml/min/1.73 m ²)	8 (12.1)	2 (3.1)	
Concomitant medications			
Angiotensin converting enzyme inhibitor	57 (86.4)	58 (89.2)	0.79
Beta-blocker	48 (72.7)	62 (95.4)	<0.001
Oral nitrate	13 (19.7)	17 (26.2)	0.41
Hydralazine	6 (9.1)	16 (24.6)	0.02
Spironolactone	12 (18.2)	25 (38.5)	0.012
Loop diuretic	61 (92.4)	46 (70.8)	<0.001
Diltiazem	4 (6.1)	1 (1.5)	0.36

Data are no. (%) of patients or mean ± SD values.

eGFR = estimated glomerular filtration rate.

^aCalculated by using the Devine equation.¹²

^bCalculated by using the Cockcroft and Gault equation.¹³

^cCalculated by using the four-variable Modified Diet in Renal Disease equation.⁴⁵

^dClassified according to the National Kidney Foundation.⁴⁶

Table 2**Digoxin Doses Received**

Daily Digoxin Dose (mcg)	Standard Care Group (n=66)	Nomogram Group (n=65)
62.5 ^a	1 (1.5)	11 (16.9)
125	39 (59.1)	36 (55.4)
250	25 (37.9)	18 (27.7)
500	1 (1.5)	0 (0)

Data are no. (%) of patients.

^a Administered as 125 mcg every other day

Table 3

Multiple Regression of Serum Digoxin Concentration Prediction Error Between the Nomogram and Standard Care Groups

Variable	Model 1		Model 2	
	Beta	P Value	Beta	P Value
Nomogram	−0.41	<0.0001	−0.62	<0.0001
Digoxin dose	3	<0.0001	2.8	<0.0001
Cl _{Cr} 50 ml/min	−0.24	0.019	−0.37	0.0015
Body mass index (kg/m ²)	−0.0086	0.045	−0.0092	0.03
Age (yrs)	0.0027	0.4	0.0033	0.31
Male sex	−0.16	0.053	−0.19	0.018
Nomogram × Cl _{Cr} 50 ml/min	—	—	0.36	0.026
Constant	0.17	0.57	0.27	0.37
N	130		130	
R ²	43		46	

Serum digoxin concentration (SDC) prediction error is defined as actual SDC −0.7

Cl_{Cr} = creatinine clearance

Table 4

Pharmacogenomic Comparisons in the 55 Patients Who Provided Genetic Samples

Variable	Wild-type	T carrier	TT	A carrier
<i>ABCB1</i> genotype frequency *				
SNP C1236T	31 (56.4)	20 (36.4)	4 (7.3)	NA
SNP C3435T	27 (49.1)	25 (45.5)	3 (5.5)	NA
SNP G2677T/A	38 (69.1)	12 (21.8)	3 (5.5)	2 (3.6)
Steady-state serum digoxin concentration (ng/ml)				
SNP C1236T	0.52 ± 0.27	0.56 ± 0.37	0.58 ± 0.29	NA
SNP C3435T	0.54 ± 0.28	0.54 ± 0.35	0.46 ± 0.07	NA
SNP G2677T/A	0.54 ± 0.27	0.50 ± 0.42	0.66 ± 0.30	0.40 ± 0.13

Data are no. (%) of patients or mean ± SD values.

SNP = single nucleotide polymorphism; NA = not applicable

None of the differences in serum digoxin concentration between genotypes were statistically significantly different within each SNP.

* Genotype distributions did not deviate from the Hardy-Weinberg Equilibrium in racial-ethnic groups.

Table 5
Associations Between *ABCB1* Genetic Variants and Steady-State Serum Digoxin Concentrations

Variable	Genetic Models							
	Model 1 (Reduced Model)	Model 2 (Additive)	Model 3 (Dominant)	Model 4 (Recessive)				
	Beta	Beta	Beta	Beta	P value	P value	Beta	P value
Digoxin dose (mcg/day)	1.778	2	2	2	0.087	0.08	2.1	0.08
Creatinine clearance (ml/min)	-0.0009	-0.0015	-0.002	-0.002	0.623	0.55	-0.0021	0.51
Body mass index (kg/m ²)	-0.00897	-0.01	-0.0095	-0.0095	0.048	0.079	-0.0075	0.12
SNP C1236T	-	-0.038	-0.014	-0.014	0.7	0.9	-0.4	0.23
SNP C3435T	-	-0.081	-0.074	-0.074	0.32	0.42	-0.27	0.17
SNP G2677T/A	-	0.014	-0.044	-0.044	0.9	0.73	0.55	0.17
Constant	0.62	0.74	0.75	0.75	0.0003	0.0004	0.64	0.0004
N	55	55	55	55				
R ²	0.19	0.22 ^a	0.22 ^b	0.24 ^c				

SNP = single nucleotide polymorphism

All models were adjusted for self-reported race-ethnicity.

^a p = 0.61 for F test for difference in R² between model 1 and model 2.

^b p = 0.71 for F test for difference in R² between model 1 and model 3.

^c p = 0.39 for F test for difference in R² between model 1 and model 4.