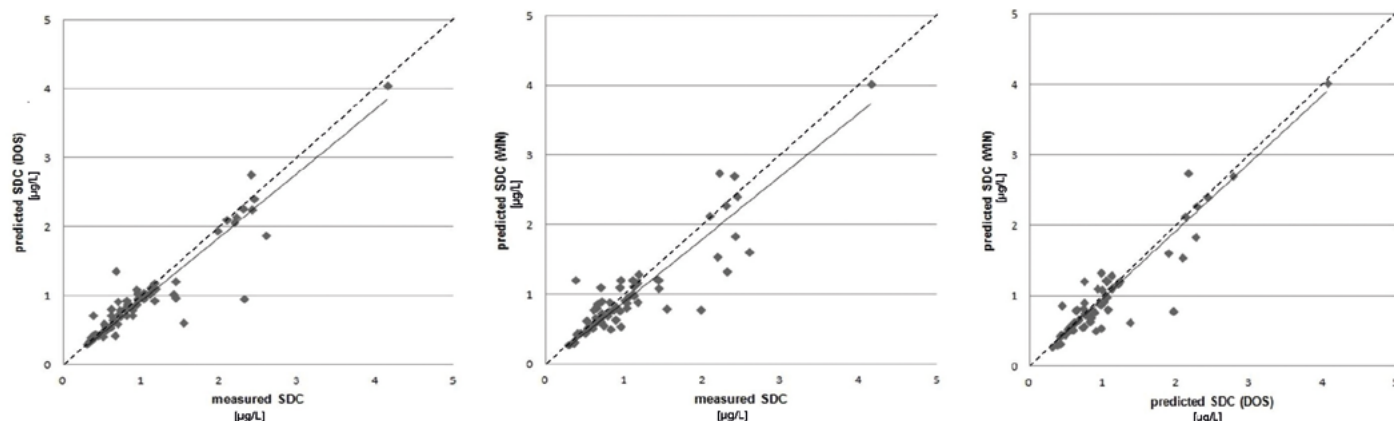


Fig. 3. Comparison of measured and predicted SDC values in DOS modela, in Windows modelb, in WIN and DOS modelc. The full line represents linear regression, while the dashed line is the line of identity ($y=x$)



evaluation. Pearson's coefficient of rank correlation was calculated. %PE was calculated as the difference between predicted and the measured value (formula 1) and as the difference between both models (formula 2). RMSE was calculated according to formula 3.

%PE = (1) %PE = (2) RMSE = (3)

Tab. 3. Plasma levels (SDC) of digoxin

Parameter	measured	predicted (DOS)	predicted (WIN)
SDC (μg/L)	0.86 (0.60–1.16)	0.88 (0.60–1.05)	0.83 (0.57–1.19)
%PE (1) (%)		-1.3 (-6.4 –7.1)	-3.2 (-11.8–7.2)
%PE (2) (%)			-0.4 (-10.2–8.6)
RMSE (%)		1.2 (0.2–1.3)	2 (0.6–2.9)

%PE was calculated as a difference between predicted and measured values (1), and as a difference between both models (2). Individualized data are presented as a median (interquartile range).

%PE: percentage prediction error; RMSE: root mean square error; SDC: serum digoxin concentration;

Statistical analysis

Statistical analysis of all data was performed using Prism 8.3.0 (GraphPad Software, San Diego, CA, USA) and MedCalc 18.2.1. (MedCalc Software, Ostend, Belgium). All values are presented as median (interquartile range). For comparison of repeated measurements of SDC's the Wilcoxon signed-rank test was used.

To make the point that methods used to measure chosen parameters had good correlation when a set of samples had been chosen, the Bland and Altman plot was used. Correlations between calculated SDC's in both models were evaluated by Pearson's correlation as appropriate. All data were analyzed on an intention-to-treat basis and for each test, a P value <0.05 was considered statistically significant.

Results

The baseline demographic, clinical characteristics laboratory findings of the study cohort are listed in Table 1. The final analysis included 29 patients.

All pharmacokinetic parameters of digoxin - populational and individualized data are summarized in Table 2. WIN uses lower absorption rate constant (k_a) (0.61 vs 2.5), and absolute bioavailability (F) (0.65 vs 0.7),

compared to DOS. Further differences were observed between total plasma clearance (CL) (6.11 vs 6.45 L/h) and extrarenal fraction (f_e) (0.771 vs 0.783). Changes in k_a and F manifested in minor differences between minimal (C_{min}) and maximal (C_{max}) concentration - narrowing of the curve, as evident from the graphic output of both models - for DOS (Fig 1a) and for Windows (Fig 1b). It was obvious that WIN predicted lower values of pharmacokinetic parameters than DOS, but there were no significant differences between measured and predicted values by both versions (Table 3).

The distribution of error on Bland-Altman analysis of measured and predicted SDC is given in Fig 2a (for DOS) and Fig 2b (for Windows). The distribution of errors of predicted SDC in both models is given in Fig 2c. As it is shown, most points lie inside the limits which indicates that there is agreement between the models.

Comparison of measured and predicted values of SDC is given in Fig 3a (for DOS) and Fig 3b (for WIN). Comparison of predicted values of SDC in both models is given in Fig 3c. There was a close correlation between predicted and measured SDCs (the Pearson's coefficient of correlation was

0.008 for DOS vs 0.314 for WIN model, both $P<0.0001$) and between SDCs predicted by both models (0.013, $P<0.0001$).

Discussion

To our knowledge, this study is the first one evaluating quality of the long-term prediction of serum drug levels achieved by two different versions of the same TDM software package. We demonstrated that formerly popular, long-term used, but in these times unsupported DOS version of the MwPharm software can be used for TDM of digoxin interchangeably with actually used Windows version - dosing advice will not be affected regardless of the chosen version.

TDM of digoxin has been used for more than 50 years [10]. Based on the published studies, it is considered appropriate to target a SDC in the therapeutic range of 0.5 to 2 μg/L, but there is a large interindividual variability [15]. The risk of digitalis intoxication (ADRs) increases at serum concentrations of ≥ 2.0 μg/L [10]. The purpose of blood concentration monitoring of digoxin is the prevention of ADRs, especially extracardiac ADRs, and digoxin should be administered at minimum effective concentrations. SDC at 0.5–0.9 μg/L reduces mortality and hospitalizations in all HF