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ARTICLE

Population Pharmacokinetics of Candesartan in Patients with Chronic Heart Failure

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Heart failure (HF) causes pathological changes in multiple organs, thus affecting the pharmacokinetics (PK) of drugs. The aim of this study was to investigate the PK of candesartan in patients with HF while examining significant covariates and their related impact on estimated clearance using a population PK (Pop-PK) modeling approach. Data from a prospective, multicenter study were used. Modeling and simulations were conducted using Nonlinear Mixed-Effects Modeling (NONMEM) and R software. A total of 281 white patients were included to develop the Pop-PK model. The final model developed for apparent oral clearance (CL/F) included weight, estimated glomerular filtration rate (eGFR), and diabetes, which partly explained its interindividual variability. The mean CL/F value estimated was 7.6 L/h (1.7–22.6 L/h). Simulations revealed that an important decrease in CL/F (> 25%) is obtained with the combination of the factors retained in the final model. Considering these factors, a more individualized approach of candesartan dosing should be investigated in patients with HF.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Heart failure (HF) could affect the pharmacokinetics (PK) of drugs. Despite being a widely used treatment for HF, the PK of candesartan was investigated to a limited extent in patients with HF.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Using a population approach, this study characterized the PK of candesartan in patients with HF while identifying covariates influencing the apparent oral clearance (CL/F) of candesartan.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Patients having low body weight with moderately to severely impaired renal function, and patients with diabetes with mildly to moderately impaired renal function presented an important decrease in candesartan CL/F. Patients having these combinations of factors achieved comparable concentrations to the rest of the patients despite receiving lower doses. They also experienced greater increases in serum potassium compared with other patients, but similar improvements in N-terminal pro B-type natriuretic peptide.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ In a specific subpopulation of patients with HF, it may not be necessary to achieve the target doses of candesartan. Thus, a more individualized dosing approach is needed in patients with HF. This hypothesis requires validation in a prospective clinical trial.

Heart failure (HF) affects > 26 million people worldwide.[1] It is a complex clinical syndrome that involves changes in several physiological pathways that can affect other organs, such as the kidneys, blood vessels, and the liver.[2] The activation of the renin-angiotensin-aldosterone system plays a central role in HF physiopathology by causing sodium retention, inflammation, cardiac arrhythmia, and fibrosis.[3] Accordingly, the angiotensin II receptor blocker candesartan proved to be an effective drug decreasing morbidity and mortality in trials of patients with symptomatic HF.[4] Despite its widespread use in the treatment of HF, the pharmacokinetics (PK) of candesartan have been previously investigated only to a very limited extent in patients with HF.[5]

Candesartan is administered orally as the prodrug candesartan cilexetil that is rapidly and completely hydrolyzed by carboxylesterase during its absorption in the intestinal tract to the active metabolite candesartan. Estimated bioavailability for candesartan is 15%. Because this metabolite is highly bound to plasma proteins, its volume of distribution is quite low (0.13 L/kg). Candesartan is inactivated to a small extent by hepatic metabolism (CYP2C9) and primarily eliminated unchanged via the urinary and biliary tracts.[6]

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Given that HF induces changes in the function of several organs, our primary objective in this study is to characterize, using a population approach, the PK of candesartan in patients with HF, and to identify covariates that could partly explain interindividual variability in observed clearance. Moreover, as recently underscored by a position statement by the European Society of Cardiology (ESC), given the potential sex differences in the PK of drugs,[7] we also investigated candesartan clearance separately in men and women.

METHODS

Study design and patient's characteristics

We performed a population pharmacokinetics (Pop-PK) substudy of a previously reported prospective pharmacogenomic study. The study design and patient's population have been described in detail previously.[8] Briefly, patients with symptomatic HF (left ventricular ejection fraction ≤ 40% and New York Heart Association functional classes II–IV) were recruited at 16 Canadian centers to participate in an open-label nonrandomized study that included 4 visits for titration and an additional 2 visits for treatment (0, 2, 4, 6, 8, and 16 weeks). Patients' clinical stability was evaluated (including blood pressure, serum creatinine, and potassium), and their candesartan cilexetil dose was escalated at each titration visit (4, 8, 16, and 32 mg once daily) if the previous dose was tolerated. During the first visit, all patients received a dose of 4 mg of candesartan cilexetil, and after 2 hours, blood samples were collected to measure candesartan concentrations. The PK sampling was then performed at each follow-up visit and timing in regard to the previous dose was dependent on the timing of the study visit.

Cardiovascular biomarkers (N-terminal pro B-type natriuretic peptide (NT-ProBNP), B-type natriuretic peptide (BNP), renin mass, renin activity, and aldosterone) were measured at baseline and at the end of the study, as previously published.[8] Candesartan concentrations were measured using liquid chromatography-mass spectrometry. Plasma concentration measurements ranged from 1.00 to 250 ng/mL. If the concentration exceeded 250 ng/mL, samples were reanalyzed using 10-fold dilution. We limited our investigation to the white patients included in the study who had at least one candesartan concentration measured within 30 hours after the administration of a documented candesartan cilexetil dose, and regardless of genomic sampling availability. As previously reported,[8] the study was approved by all local institutional review boards and all patients provided a written consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki with Good Clinical Practice.

Population pharmacokinetic analysis

PK model development. The PK modeling was performed with Nonlinear Mixed Effect Modeling software (NONMEM), version 7.4 (GloboMax, ICON Development Solutions, Ellicott City, MD) using first-order conditional estimation with interaction algorithm. As a first step, a structural PK model (without covariates) was developed, assuming a log-normal distribution of PK parameters with an exponential interindividual variability:

$$\theta = P_{TV} * \mathrm{EXP}^{\eta}$$

where θ represents the individual value of the parameter predicted by the model, P_{TV} is the parameter's typical value in the population, and η representing interindividual variability. PK parameters maximizing the likelihood of the observations were estimated. These observations Y_{ij} are described by the following equation:

$$Y_{ij} = F_{ij} + \varepsilon_{ij}$$

where F_{ij} is the plasma concentration for the i-th subject at time t_j predicted by the model, and ε_{ij} its residual (random) variability. This random effect could be modeled with several forms:

(i) Additive, where the variability remains constant with the concentrations ($\varepsilon_{ij} = \varepsilon 1_{ij}$)
(ii) Proportional, where the variability changes proportionally with the concentrations ($\varepsilon_{ij} = F_{ij}{*}\varepsilon 2_{ij}$)
(iii) Mixed, which is the combined form of the two previous cases ($\varepsilon_{ij} = \varepsilon 1_{ij} + F_{ij}{*}\varepsilon 2_{ij}$).

After developing this model, the potential role of covariates in explaining interindividual variability in PK parameters was examined. Twenty-six covariates were considered: sex, age, weight, height, body mass index, left ventricular ejection fraction, New York Heart Association (NYHA) class, the presence of comorbidities (hypertension, diabetes, and atrial fibrillation), the use of concomitant drugs (digoxin, beta blockers, furosemide, spironolactone, and lipid-lowering agents), aldosterone level, renin mass, renin activity, BNP, NT-ProBNP, C-reactive protein, estimated glomerular filtration rate (eGFR), systolic blood pressure, diastolic blood pressure, serum potassium, and CYP2C9 inferred metabolizing capacity.

To minimize the potential of type-I error due to the high number of candidate covariates, we performed a preliminary selection of covariates using statistical tests. Univariate linear regression was applied on the continuous covariates as independent variable and $\eta_{\text{PK parameter}}$ as dependent variable ($P < 0.05$) and analysis of variance was applied on the categorical covariates as independent variable and $\eta_{\text{PK parameter}}$ as dependent variable ($P < 0.05$).

A stepwise forward-backward selection approach was performed on the preliminarily selected covariates. In the forward selection step, each covariate was separately added to the PK parameter equation. If the covariates improved the objective function with an associated $P < 0.05$, they were retained in the final-forward model. Subsequently, in the backward step, every retained covariate was separately removed from the final-forward model. If the removal of the covariate had worsened the objective function by a stricter criterion ($P < 0.001$), the covariate was retained in the final model.

The final model was used to simulate plasma concentrations of candesartan over 72 hours for each patient. Afterward, elimination half-life was calculated using log-linear least squares regression analysis of the terminal phase of the simulated concentrations time curve.

Clearance estimation and covariates examination based on the sex of the patient

In several clinical studies, sex differences in the PK of drugs, and pathophysiology of HF have been reported.[7,9,10] Thus, additional analyses were conducted to explore whether the same covariates that appeared to affect the apparent clearance (CL/F) significantly in the overall population would be selected as well in men and women separately. Therefore, the structural PK model was used to estimate the clearance separately for men and women. Subsequently, the effect of potential covariates on the apparent clearance estimated in each group was explored using the forward/backward selection approach.

Model validation

During all steps of model development, the following criteria were assessed to evaluate model adequacy: successful minimization of the objective function, condition number (ratio of the largest to smallest eigenvalues which reflects the stability of the model) < 1,000, relative standard error on PK parameters not exceeding 30%, and goodness of fit plots adequacy.[11,12]

Final model performance was evaluated using visual predictive check (VPC), where 500 replicates of concentrations' simulation were generated for the patients in the original sample: using final parameter estimates, the median, the 2.5th and 97.5th percentile of simulated concentrations were computed. These percentiles were plotted with those calculated directly from observed concentrations in the same graphic in order to visually compare their distribution consistency.

Estimations' precision was examined using the 95% confidence interval obtained with the bootstrap resampling technique. In order to have an accurate calculation of the percentiles for the confidence interval, a minimum of 1,000 samples is required.[13] In this analysis, 1,500 datasets of different combination of patients (with replacement) were created from the original dataset. Then, the final model was fitted separately to each sample, and the PK parameters were estimated each time to calculate, at the end of this process, the 95% confidence interval by choosing the 2.5th and 97.5th percentiles.

Simulation of clearance

In order to identify covariates that could eventually be helpful to personalize dosing in practice, the CL/F of patients having specific covariate values was simulated using the final model. For each set of covariate values, we used 1,000 replicates to compute the probability of having a change of > 25% in CL/F compared with the typical value estimated in the population. This threshold was selected because, given the mean dose reached in this and other similar studies,[8,14] it represented the minimal change that would enable an adjustment of 4 mg, the smallest available formulation, in the dose of candesartan. Patients expected to have a change of at least 25% in CL/F, based on the above, were identified in our database. To examine the effect of such clearance change at the dose level and PK profiles of these patients (with a change of > 25% in CL/F), we compared doses they received throughout the study and their plasma concentrations with those observed in the rest of the population using Wilcoxon's statistical test. Furthermore, we compared in these two populations the effect of candesartan on changes in NT-ProBNP, serum potassium, blood pressure, and eGFR. Comparison was performed using generalized linear model for changes in NT-ProBNP, adjusting for baseline concentrations. Given that the other markers (serum potassium, blood pressure, and eGFR) of drug response were measured at multiple timepoints, we used generalized linear model and linear mixed effects model. For these analyses, a $P < 0.05$ was considered statistically significant.

RESULTS

In total, 1,455 concentration timepoints collected from 281 white patients were used in this analysis. Baseline characteristics of the study population are included in **Table 1**. Compared with men, women had a lower body weight, height, and renin mass at baseline, as well as a lower proportion with ischemic HF and use of lipid-lowering agents ($P < 0.05$).

After examining the pairs plots (**Figure S1**), a significant correlation was found among weight, body mass index, and height, as well as between renin mass and renin activity, BNP and NT-ProBNP, and systolic and diastolic blood pressure. Consequently, weight, renin mass, NT-ProBNP, and systolic blood pressure were kept with the remaining covariates of the analysis.

Candesartan concentration data were best described by a one-compartment model with first-order absorption and first-order elimination. Adding absorption lag time in the model improved model fit, as shown by a significant decrease in objective function ($P < 0.05$). Because the drug was given orally, the following apparent PK parameters were estimated: CL/F, apparent volume of distribution (Vd/F), and absorption constant (Ka). Residual variability was modeled according to a mixed error model, as it was the best fitting error model. The use of full variance-covariance matrices on individual PK parameters did not lead to a significant reduction in objective function; thus, diagonal matrices were used.

In the preliminary selection of covariates, graphical examination and univariate statistical tests revealed a significant relationship between estimated CL/F and the following covariates: weight, age, NT-ProBNP, eGFR, diabetes, use of furosemide, and sex.

The stepwise forward-backward approach was applied on these covariates and results for the univariate developed models are presented in **Table S1** in the **Supplementary Material**.

Weight, eGFR, diabetes status, the use of furosemide, and sex were selected in the forward process because their inclusion in the model decreased the objective function by > 3.841 for 1 degree of freedom ($P < 0.05$; **Table S1**). After the backward step, use of furosemide and sex were removed because their exclusion from the model did not increase the objective function by > 10.83 for 1 degree of freedom ($P > 0.001$) giving rise to the final model for CL/F:

$$\mathrm{CL/F}\,(L/h) = 8.63 * (\mathrm{Weight}/82.45)^{0.963} * (\mathrm{eGFR}/74)^{0.56} * (0.682)^{\mathrm{Diabetes}} * \exp^{0.138}$$

Table 1 Descriptive statistics of patients' characteristics

Characteristics	Study population (*n* = 281)	Men (*n* = 233)	Women (*n* = 48)
Women, %	17	0	100
Age, years	65.6 (10.0)	65.8 (9.9)	64.7 (10.3)
Weight, kg	84.0 (19.1)	86.6 (18.5)	71.3 (16.8)*
Height, cm	159.2 (42.6)	161.4 (43.0)	148.1 (39.3)*
BMI	27.3 (9.1)	27.4 (9.0)	26.9 (9.6)
Medical history			
Left ventricular ejection fraction, %	29.2 (7.1)	29.3 (7.0)	28.9 (7.7)
NYHA functional class II/ III–IV, %	78.3/ 21.7	77.7/ 22.3	81.2/ 18.8
Ischemic etiology, %	71.9	76.8	47.9*
Hypertension, %	56.2	54.1	66.7
Diabetes mellitus, %	32.7	33.9	27.1
Atrial fibrillation, %	27.0	27.9	22.9
Systolic blood pressure	120.0 (16.0)	119.9 (16.2)	120.8 (15.1)
eGFR, mL/min/1.73 m^2	74.2 (22.3)	74.3 (22.6)	68.2 (20.5)
Normal renal function, %	20.6	22.3	12.5
Mild renal dysfunction, %	48.4	48.5	47.9
Mild to moderate renal dysfunction, %	20.6	20.6	20.8
Moderate to severe renal dysfunction, %	10.3	8.6	18.1
Concomitant drugs			
Digoxin, %	26.0	27.5	18.8
Beta blockers, %	93.6	93.6	93.8
Furosemide, %	71.9	71.2	75.0
Spironolactone, %	23.1	24.5	16.7
Lipid lowering agents, %	84.7	86.7	75.0*
Potassium supplements, %	11.7	11.6	12.5
Biomarkers			
NT-ProBNP, ng/L	1,291.9 (1,818.1)	1,182.3 (1,568.2)	1,822.0 (2,684.4)
CRP, mg/L	4.1 (8.6)	3.8 (8.0)	5.7 (10.7)
Renin mass, ng/L	140.3 (238.7)	148.7 (243.0)	99.6 (215.0)*
Aldosterone, ng/L	180.6 (105.6)	177.7 (107.0)	194.5 (98.7)

BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NT-ProBNP, N-terminal ProBNP; NYHA, New York Heart Association.
Data presented as mean (SD) or %.
Statistical analysis performed with Wilcoxon test, *t*-test, and χ^2 test.
Normal renal function: eGFR ≥ 90 mL/min/1.73 m^2; mild renal dysfunction: 60 ≤ eGFR < 90 mL/min/1.73 m^2; mild to moderate renal dysfunction: 45 ≤ eGFR < 60 mL/min/1.73 m^2; moderate to severe renal dysfunction: eGFR < 45 mL/min/1.73 m^2.
*$P < 0.05$.

PK parameters estimated in the final model are summarized in **Table 2**. Moreover, an elimination half-life of 6.2 hours (range 4–18 hours) was obtained.

Clearance estimation and covariates examination based on the sex of the patient

Using our structural model, CL/F was estimated to be 7.96 L/h in men vs. 5.9 L/h in women ($P < 0.01$). After examining the covariates by forward/backward selection approach, weight, eGFR, and diabetes were also found to be significant for men ($n = 233$), but no variables reached statistical threshold in women ($n = 48$).

Model evaluation

Goodness of fit. Goodness of fit plots for the final PK model are shown in **Figure 1**. In these plots, it can be observed that the blue tendency line is close to the black identity line, indicating that there is no significant departure from the identity line between observed and predicted concentrations. Furthermore, on the right-hand side, conditional weighted residuals (CWRES) appear to be centered around 0 and dispersed approximately in a constant manner between [–5 and +5], but with a slight trend over population predictions and time after dose. These diagnostic results support the conclusion that overall, the final model describes well the candesartan data collected in patients with HF.

Visual predictive check. Because the majority of observations were measured between 0 and 4 hours postdose (**Figure S2**), the calculation of the median, percentiles 2.5 and 97.5 after 4 hours was not possible due to lack of observations. Therefore, the final model performance was evaluated with a VPC performed between 0 and 4 hours postdose (**Figure 2**). In this time range, the observed concentrations (solid line) are within

Table 2 Parameter estimates of the final population pharmacokinetic model

Model parameters	Estimates	RSE, %
CL/F - θ_1 (L/h)	8.63	4
Vd/F - θ_2 (L)	12.5	10
Ka - θ_3 (h^{-1})	0.131	6
T_{LAG} - θ_4 (h)	0.165	3
Covariates effect		
Weight effect on CL/F - θ_5	0.963	15
eGFR effect on CL/F - θ_6	0.56	18
Diabetes effect on CL/F - θ_7	0.682	8
Interindividual variability		
$\omega^2_{CL/F}$	0.138	7
Residual variability		
$\sigma^2_{(additive)}$	5.5	20
$\sigma^2_{(proportional)}$	0.418	3

CL/F, apparent oral clearance; eGFR, estimated glomerular filtration rate; F, bioavailability; Ka, absorption constant; RSE, relative standard error; T_{LAG}, lag time; Vd/F, apparent volume of distribution.
θ_1: Candesartan oral clearance value in the population for a median weight of 82.45 kg and a median eGFR of 74 mL/min/1.73 m^2, $\omega^2_{CL/F}$: Interindividual variance estimate for apparent oral clearance, σ^2: Residual error variance.

the prediction interval (blue shade). Thus, the distribution of the observations is consistent with that of predictions.

Bootstrap. Bootstrap resampling results are summarized in **Table 3**. PK parameter values estimated in the final model are within 15% of the mean parameter estimates obtained from bootstrap samples. Furthermore, PK parameters' confidence intervals are narrow and contain final model estimations. Thereby, these latter were considered to be precise.

Simulation of clearance

The final model was used to simulate oral clearance for patients having the following covariate values: being diabetic, weighing 60 kg, 70 kg, 90 kg, having an eGFR of 45, 60 mL/min/1.73 m^2, or a combination of these. The changes to the typical oral clearance are summarized in **Figure 3**. A change within 25% is represented as the blue zone in **Figure 3**. The numbers outside this zone represent the probability of having a change in CL/F of > 25%. Indeed, by simulating patients with diabetes, patients with a weight of 60 kg, or an eGFR of 45 mL/min/1.73 m^2, there was, respectively, a 90%, 65%, and 42% probability that CL/F of candesartan will decrease by > 25%. On the other hand, for the remaining covariate values explored in these simulations, the effect was below this threshold.

We also evaluated how the combination of these factors could influence the CL/F of candesartan. Given that patients with diabetes are most often overweight, a combination of diabetes with low body weight was not examined. For example, in the current study, only three patients were found to be diabetic with low body weight. For the 2 cases of covariate combinations that were simulated, a high probability of having a change in CL/F of > 25% was observed.

In our database, 43 patients with these combinations of covariates were identified (referred as predicted

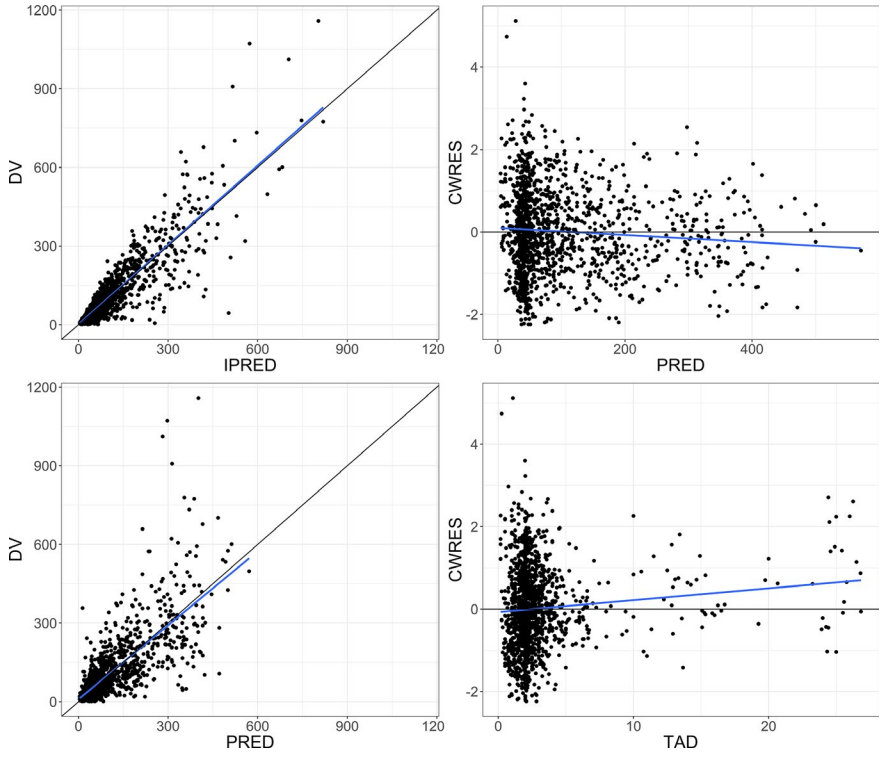

Figure 1 Goodness of fit plots. Left-hand side: Plots of observations (DV: dependent variables) vs. individual predictions (IPRED) or population predictions (PRED). Right-hand side: Plots of conditional weighted residuals (CWRES) vs. population predictions or time after dose (TAD).

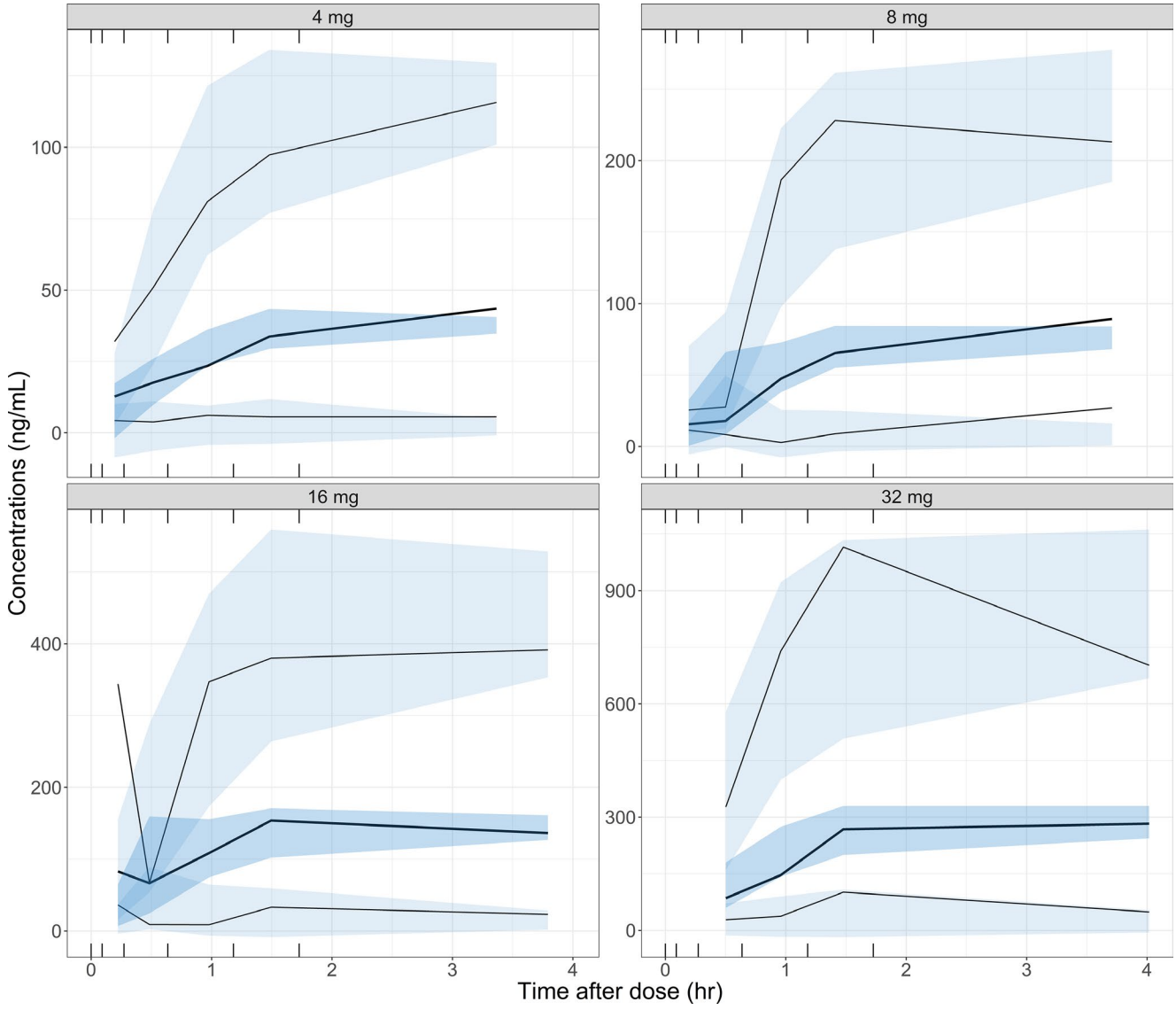

Figure 2 Visual predictive check stratified by dose and performed between 0 and 4 hours postdose. Black solid lines represent (from bottom to top) the 2.5th, 50th, and 97.5th percentiles of the observations. Blue areas refer (from bottom to top) to the 95% confidence intervals for the same percentiles, as predicted by the model.

Table 3 Bootstrap results and parameter estimates of the final population PK model

Parameters	Final model estimations	Bootstrap mean	95% CI
CL/F, L/h	8.63	8.60	7.89–9.42
Vd/F, L	12.5	12.10	8.52–16.80
Ka, h^{-1}	0.131	0.129	0.109–0.153
T_{LAG} (h)	0.165	0.205	0.049–0.387
Weight effect on CL/F - $\theta 5$	0.963	0.955	0.642–1.250
eGFR effect on CL/F - $\theta 6$	0.56	0.56	0.36–0.77
Diabetes effect on CL/F - $\theta 7$	0.682	0.679	0.556–0.805

CI, confidence interval; CL/F, apparent oral clearance; eGFR, estimated glomerular filtration rate; F, bioavailability; Vd/F, apparent volume of distribution; Ka, absorption constant; T_{LAG}, lag time.

low-clearance population). The results of the comparison of the doses received throughout study visits and the concentration measurements, performed between this predicted low-clearance population and the rest of the patients, are presented in **Table 4**. Predicted low-clearance population characteristics are presented in **Supplementary Table S2**.

Two hours after receiving the first dose (4 mg), although no significant difference in the concentrations was observed, the predicted low-clearance population presented a numerically higher candesartan concentration. After 2 weeks (visit 2), this difference in the concentrations was statistically significant between the 2 populations, despite patients still receiving the same dose.

At the fourth, sixth, and eighth week, there was no statistically significant difference in concentrations, but, by that time, the predicted low-clearance population was less

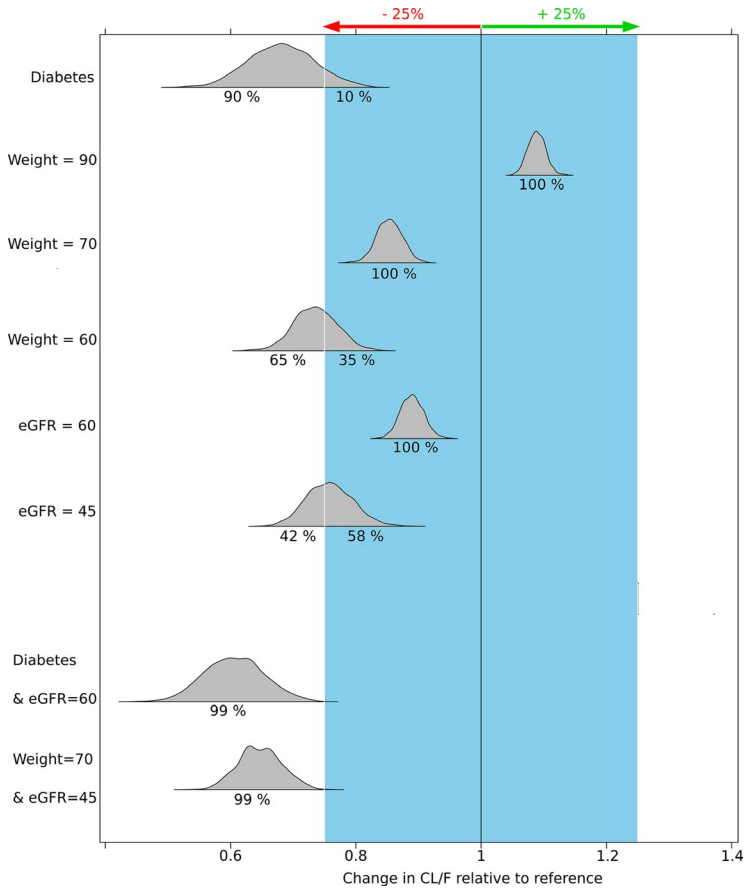

Figure 3 Covariates effect on the typical value of apparent oral clearance (CL/F). Black solid line in the middle of the blue zone corresponds to the typical value of the CL/F estimated in our study population. Blue shaded zone represents a change within 25% in CL/F. Numbers outside this zone represent an approximation of the probability to have a change of > 25% in CL/F relative to the typical value. Numbers inside this zone represent an approximation of the probability to have a change of < 25% in CL/F relative to the typical value. Diabetes: Simulated patients with diabetes; weight = 90: Simulated patients weighting 90 kg; weight = 70: Simulated patients weighting 70 kg; weight = 60: Simulated patients weighting 60 kg. Estimated glomerular filtration rate (eGFR) = 60: Simulated patients having an eGFR of 60 mL/min/1.73 m^2; eGFR = 45: Simulated patients having an eGFR of 45 mL/min/1.73 m^2. Diabetes & eGFR = 60: Simulated patients with diabetes with an eGFR of 60 mL/min/1.73m^2. Weight = 70 & eGFR = 45: Simulated patients weighing 70 kg with an eGFR of 45 mL/min/1.73m^2.

Table 4 Comparison of the doses received throughout visits and the concentrations between the predicted low-clearance population and the other patients

Predicted low-clearance population	Total	Time	Mean dose, mg (SD)	Mean concentrations, ng/mL (SD)
No	208	Week 0 (2 hours postdose)	4 (0)	44 (34)
Yes	38		4 (0)	52 (33.3)
No	219	Week 2	4 (0)	41 (25.4)
Yes	41		4 (0)	53 (28.5)*
No	212	Week 4	6.9 (1.8)	76 (54.4)
Yes	35		5.8 (2)*	91 (54)
No	213	Week 6	11.6 (5.2)	115.0 (85.4)
Yes	32		8.7 (5.2)*	107.0 (90.4)
No	204	Week 8	19.4 (11.7)	183.0 (162.4)
Yes	32		14.1 (12.0)*	207.0 (221.0)
No	195	Week 16	19.6 (12.2)	167 (172.0)
Yes	26		15.4 (12.1)	156 (170.4)

Predicted low-clearance population: Patients with a combination of covariates that lead to a reduction of more than 25% in apparent oral clearance: patients with diabetes having an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2; patients weighing ≤ 70 kg and having an eGFR ≤ 45 mL/min/1.73 m^2. Statistical analysis performed with Wilcoxon test.
*$P < 0.01$.

likely to have undergone or tolerated dosing titrations, thus receiving lower candesartan doses compared with the rest of the patients. The proportion of patients who completed the study was also lower in the predicted low-clearance population (60.5%) compared with the other patients (81%, $P < 0.05$). At the last visit, although a similar trend in candesartan dosing differences was observed, it was no longer statistically significant.

As for pharmacological response to candesartan, similar changes in NT-ProBNP, blood pressure, and eGFR values were found between the two populations ($P > 0.05$). However, a greater increase in potassium level was reported in the predicted low-clearance population ($P < 0.05$). Detailed tables of these results are presented in **Supplementary Tables S3 and S4**.

DISCUSSION

To our knowledge, this is the first study that evaluates the clearance of candesartan, and the effect of multiple potential determinants of this parameter in patients with chronic HF using a Pop-PK modeling approach. Previously, the Pop-PK of candesartan have been studied solely in patients with hypertension, and a more limited number of covariates was available for analysis.[15,16]

In this study, we found that diabetes, weight, and renal function are key determinants of candesartan clearance. Although women had a lower clearance than men, sex was not an independent predictor of candesartan clearance after controlling for these factors. Our results suggest that considering these simple clinical characteristics could help individualize dosing of candesartan during titration in patients with HF, while achieving comparable concentrations.

In our study, candesartan data were best described by a one-compartment model with first-order absorption, first-order elimination, mixed error model, and absorption lag time. The mean value of CL/F estimated by the structural model in this population was 7.6 L/h (0.1 L/h/kg, range 1.7–22.6 L/h; 7.96 in men and 5.9 L/h in women), which is lower than the value estimated in patients with hypertension (14.1 L/h, range 3.4–28.4 L/h)[16] and healthy volunteers (0.14–0.2 L/h/kg, range 3.4–28.4 L/h).[6,17] This reduction in CL/F could be explained by (i) an alteration of the activity of the nephrons due to a chronic decrease of the renal flow caused by the reduction of cardiac output, and/or by (ii) liver congestion, caused by HF.[5,18]

In our final model, candesartan CL/F decreased when weight or eGFR decreased or in the presence of diabetes. Because candesartan is partly eliminated by the kidneys, one should expect that the total clearance will be affected by the eGFR, which is confirmed in our final model. Furthermore, our simulations showed that an important decrease in eGFR is needed to obtain a significant reduction in CL/F (> 25%).

Diabetes is a frequent comorbidity in patients with HF. Indeed, it is an important risk factor of adverse cardiovascular events while being associated with a higher incidence of side effects of renin-angiotensin-aldosterone system modulating drugs, particularly the risk of hyperkalemia.[19,20]

More severe renal dysfunction leading to higher drug concentrations has traditionally been hypothesized to be a key factor behind this association.[21] Yet, our simulation results suggest that the impact of diabetes on candesartan clearance goes beyond renal dysfunction. One possible explanation could be that eGFR simply does not perfectly reflect renal function. Another possibility is that by affecting the micro-circulation and the macro-circulation, and due to insulin resistance, diabetes could also alter hepatic function and bile flow.[22] However, further investigations are required (e.g., physiologically-based pharmacokinetics modeling) to better understand how diabetes decreased the clearance of candesartan in HF.

Several studies revealed that weight is a significant covariate for different drug clearance.[23] Furthermore, a recent expert position paper by the European Society of Cardiology on the impact of body mass on clinical events and antithrombotic regimens highlighted that underweight patients are at higher risk of overdose and adverse drug reaction, such as bleeding, following fixed dose intake.[24] In agreement with these results, we found that patients with low body weight are more likely to have a significant reduction in candesartan CL/F. These findings support the importance of considering weight in optimizing drug dosing strategies.

As part of this study, we performed simulations to explore the potential impact of the significant factors on the CL/F of candesartan. In fact, these simulations revealed a reduction of > 25% in CL/F in patients having low body weight with moderately to severely impaired renal function, and in patients with diabetes with mildly to moderately impaired renal function. Patients meeting these criteria (referred as predicted low-clearance population) were identified and examined in our database (43 patients).

After a single dose (4 mg once daily), no significant difference in concentrations was observed between the predicted low-clearance population and the rest of the patients. This could be explained by the fact that these concentration measurements were performed in the absorption phase, only 2 hours after the first dose. Thus, a change in clearance will barely affect the concentrations profiles measured at this time. Yet, numerical trends were already apparent. After 2 weeks, steady-state was reached and higher concentration levels were observed in the predicted low-clearance population, despite similar dose intake. In fact, in these patients, candesartan dosing titrations were not possible to an extent similar to the rest of the patients. Indeed, following the titration (week 8) and at the last study visit (week 16), differences of 4 to 5 mg in candesartan doses were apparent between the groups. At the last visit, this difference in candesartan dose (and concentration) was not statistically significant between the two populations of patients. This could be explained by the fact that a lower percentage of patients was able to complete the study (until the last visit) in the predicted low-clearance population (60.5%) compared with other patients (81%, $P < 0.05$). Therefore, these observations suggest that, in clinical practice, a dosage adjustment could be performed in patients with HF presenting these combinations of factors, or, at least, their status should be more closely monitored (especially potassium) after initiation of candesartan and during dose titration.

Although this hypothesis requires validation, our results could have a significant impact on clinical practice.

In patients with HF, drugs are generally titrated slowly over several outpatient visits, from a low initial dose, to reach a target dose. Besides, the clinical guidelines put significant emphasis on achieving these doses. Thus, considerable effort is invested in the dose titration process. This process often requires a back and forth between increasing and decreasing the dose to ensure tolerability.[25,26]

Our results suggest that in a specific predicted low-clearance subgroup of individuals, a candesartan concentration comparable to that of other patients could be obtained, but by using doses ~ 25% lower. Although the clinical benefit of integrating dosing adjustments of such magnitude requires validation, our results suggest that it may not be necessary to achieve the target doses of candesartan in these patients. They also suggest that aggressive titration of the drug in these subjects could lead to unnecessary titration visits and, potentially, unnecessary risk of adverse drug reactions. Therefore, a more individualized approach of drug titration should be investigated in patients with HF.

In recent years, more consideration has been given to potential differences in drug PK and response between women and men. Our findings do indeed support that candesartan clearance significantly differs between the two sexes. Although our multivariate model showed that sex was not an independent predictor of candesartan clearance, it is important to interpret the result of this multivariate model, not just from a statistical perspective, but a clinical one. Indeed, whereas from a purely statistical perspective, low weight, low eGFR, and diabetes were the independent factors reducing candesartan clearance, it is well-established that these characteristics are overly represented in women with HF.[27,28] Concordant with this extensive body of literature, in our study population, we observed a significantly lower weight in women than in men, a trend toward having a lower eGFR, but a nonsignificant lower prevalence of diabetes, which may be the result of the limited number of women included. Thus, these factors may contribute to the higher risk of adverse drug reactions reported with multiple cardiovascular drugs in women.[7] These results also highlight the need to increase the inclusion of women in dose-finding studies. In fact, the limited number of women included in this study restricted our ability to perform a properly powered investigation of the predictors of candesartan clearance specifically in women. Hence, there is a potential risk that sex-specific difference in the impact of covariates may go unrecognized. In this context, as expected, variables identified in men were consistent with those found in the overall population.

Although our study included a large number of patients with high variability in covariates, it is still subjected to certain limitations. First, the majority of the observations were measured between 0 and 4 hours postdose, which created a certain imbalance in our database that prevented the completion of the VPC after 4 hours of the dose, and probably affected the estimation of the peak concentration that seems slightly overpredicted for some patients (**Figure 1**: CWRES vs. population prediction). Second, the time of the last dose taken might be reported with less precision by the patients at sampling visits that occurred at a later time (> 20 hours postdose). The imbalanced distribution of concentration measurements along with these uncertainties resulted in a slight bias that appeared in CWRES with increasing time after dose in **Figure 1**. Furthermore, only CL/F could be estimated because no reference intravenous data were available making the absolute oral bioavailability of candesartan unidentifiable. Another limitation from our study is that its results cannot be extrapolated to patients without HF. Indeed, HF itself could modify the PK of drugs and patients with HF present multiple comorbidities that can influence the PK and response to drugs.[5] Moreover, the titration approaches of candesartan in patients with HF and hypertension somewhat differ. Specifically, contrary to HF (target dose: 32 mg daily), no target dose is recommended in hypertension.[29,30] Rather, the dose is adjusted according to a blood pressure goal, which is determined by the presence or absence of comorbidities in each patient.

In conclusion, using a Pop-PK modeling approach, we showed that the weight, eGFR, and the presence of diabetes as comorbidity were the main sources of candesartan clearance variability. Furthermore, a combination of these covariates may lead to a reduction of > 25% in CL/F. Whether a more individualized dosing approach in clinical practice integrating these factors improves clinical outcomes requires further investigation in a prospective clinical trial.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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