Population Pharmacokinetics of Ticagrelor during Veno-Arterial ECMO in Acute Coronary Syndrome: Model-Informed Dosing Simulations

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Although patients with acute coronary syndrome supported by veno-arterial extracorporeal membrane oxygenation (VA-ECMO) have a high risk of thrombosis and bleeding, antiplatelet pharmacology in this setting is not well defined. This prospective observational study investigated the population pharmacokinetics of ticagrelor and its active metabolite AR-C124910XX and explored model-informed dosing strategies among this population. Paired pharmacokinetic sampling was performed at predefined time points during ON- and OFF-ECMO periods. Plasma concentrations were measured using a validated liquid chromatography–tandem mass spectrometry assay and analyzed with NONMEM to develop a joint parent–metabolite model and evaluate the effects of VA-ECMO status and flow rate on ticagrelor disposition. Monte Carlo simulations of various ECMO flow-rate scenarios examined alternative loading and maintenance regimens using prespecified trough concentrations of 180–360 ng/mL, as derived from previous exposure–response and exposure-bleeding analyses in non-ECMO populations. A total of 225 ticagrelor and 225 metabolite concentrations (127 ON-ECMO and 98 OFF-ECMO) from 20 patients were analyzed. VA-ECMO support was associated with reduced ticagrelor clearance and increased volume of distribution, while higher flow rates were associated with decreased volumes of distribution. In simulations, an initial loading dose of 120–135 mg followed by a 60 mg maintenance dose once daily most consistently maintained predicted trough concentrations within the target range during VA-ECMO, whereas 90 mg once daily frequently exceeded the upper bound. These findings indicate that VA-ECMO substantially altered ticagrelor pharmacokinetics and provided quantitative, model-informed support for reduced once daily dosing strategies; however, further pharmacokinetic-pharmacodynamic and outcome studies are needed to confirm these findings.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Patients with acute coronary syndrome (ACS) supported by veno-arterial extracorporeal membrane oxygenation (VA-ECMO) are at high risk of both thrombosis and bleeding, but the pharmacokinetics and optimal dosing of antiplatelet agents in this setting remain poorly defined.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study characterized the pharmacokinetic changes of ticagrelor during and after VA-ECMO using population pharmacokinetic modeling and explored model-informed dosing strategies in patients with ACS requiring VA-ECMO support.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Model-based simulations suggested that regimens including a loading dose of 120–135 mg followed by a once-daily maintenance dose of 60 mg maintained predicted trough ticagrelor concentrations within the prespecified target range more consistently than standard dosing.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These findings provide a quantitative framework for model-informed ticagrelor dose individualization in patients with ACS supported by VA-ECMO and generate hypotheses that warrant prospective PK-PD and outcome validation in this high-risk population.

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Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a mechanical support system that temporarily replaces cardiopulmonary function in patients with cardiac failure, such as refractory cardiogenic shock caused by acute myocardial infarction (AMI).[1,2] It operates by entraining blood into an external ECMO circuit, which includes components such as cannulas, long tubing, and a membrane gas exchanger to facilitate gas exchange and deliver oxygenated, warmed blood into the systemic circulation.[3]

The pharmacokinetics (PK) of drugs can be altered by various factors during ECMO.[4] Patients receiving VA-ECMO have an unstable hemodynamic status because of hypoperfusion and hypoxia caused by cardiac dysfunction.[2] Therefore, several interventions, including fluids, inotropes, and vasopressors, are needed to obtain optimal filling pressure,[5] which may increase the clearance (CL) of drugs.[6] Furthermore, the decreased organ function associated with non-pulsatile blood flow in VA-ECMO could contribute to decreased CL by the reduced metabolism of drugs in the liver or kidneys.[7,8] Additionally, increased vascular permeability diminishes albumin synthesis, and increased albumin catabolism causes hypoalbuminemia in critically ill patients receiving ECMO. Thus, the volume of distribution (Vd) of high protein-binding drugs is increased by elevating the unbound fraction of drugs.[4,9] Moreover, the Vd of drugs can be increased by sequestration in the ECMO circuit, depending on their lipophilicity or the circuit material.[10,11] Therefore, drug choice and an optimal dosage regimen based on evidence are recommended to attain safety and efficacy in critically ill patients receiving ECMO.[12]

Dual antiplatelet therapy comprising aspirin and a P2Y12 inhibitor is recommended as the standard medical treatment for acute coronary syndrome (ACS).[13–15] Although ticagrelor, a reversible P2Y12 inhibitor, is associated with a higher bleeding risk than clopidogrel, recent guidelines for managing ACS recommend it as the preferred agent owing to its superior antiplatelet efficacy. Ticagrelor is metabolized by CYP3A4 in the liver to the active metabolite AR-C124910XX, which constitutes ~30–40% of the concentration of ticagrelor exposure, and the two compounds are almost equipotent.[16] The high protein-binding affinity (>99%) and lipophilic property of ticagrelor may also affect drug PK.[16,17] Furthermore, patients on ECMO have a high possibility of PK change, which can alter the blood concentrations of ticagrelor and its active metabolite, as described above.

Patients receiving VA-ECMO have substantial baseline risks of both bleeding and thrombotic complications, making antiplatelet therapy particularly challenging.[1] Contact with the circuit triggers platelet consumption and dysfunction, and bleeding has been reported in 40.8% of patients receiving VA-ECMO (95% CI, 26.8–56.6).[18] Notably, these bleeding complications are associated with significantly reduced 90-day survival.[19] In current practice, ticagrelor dosing is largely extrapolated from non-ECMO populations.[13–15] However, given the potential for circuit sequestration and critical illness-associated physiologic changes to alter drug exposure,[4,9–11] the safety and adequacy of standard dosing cannot be guaranteed in this high-risk setting. Despite this, to the best of our knowledge, no clinical PKstudy has specifically evaluated ticagrelor and its active metabolite in patients receiving VA-ECMO.

Accordingly, we hypothesized that VA-ECMO support would alter the PK of ticagrelor and its active metabolite AR-C124910XX. This prospective study was designed to characterize the population PK of ticagrelor and its active metabolite during and after VA-ECMO support and to propose an optimal dosing regimen that may reduce ischemic and bleeding complications in this setting.

METHODS

Study design and participants

This prospective observational cohort study was conducted from October 2015 to April 2018 in the coronary intensive care unit of Severance Hospital, a tertiary academic hospital in Seoul, Republic of Korea, and included consecutively enrolled patients > 19 years of age with ACS receiving ticagrelor during and after VA-ECMO. The exclusion criteria were as follows: pregnancy and/or use of strong cytochrome P450 (CYP) inducers (carbamazepine, phenytoin, rifampin, St. John's wort) or inhibitors (clarithromycin, itraconazole, ketoconazole, and lopinavir/ritonavir).

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and reported in accordance with the STROBE guidelines. The study protocol was approved by the Severance Hospital Institutional Review Board (IRB No. 4-2014-0919) and registered at ClinicalTrials.gov (NCT02581280). Written informed consent was obtained from all participants or their legally authorized representatives prior to inclusion.

ECMO system

The VA-ECMO machine was comprised of a centrifugation pump with controller (Capiox SP-101; Terumo Inc., Tokyo, Japan), air-oxygen mixer (Sechrist Ind., Anaheim, CA, USA), and conduit tube (Capiox EBS Circuit with X coating; Terumo Inc.). Femoral-femoral peripheral cannulation with 17-Fr arterial and 21-Fr venous cannulas (BioMedicus Medtronic Inc., Minneapolis, MN, USA) was used to connect to the ECMO system.

Data collection and sample analysis

The following data were recorded from patient medical records during sampling: sex, age, height, weight, smoking status, blood chemistry (blood urea nitrogen [BUN], serum creatinine [SCR], uric acid [UA], total protein [TP], albumin [ALB], and total bilirubin [TB]), ECMO factors (time to start ECMO [TTSE], duration of ECMO [DURA], ECMO flow rate, and ECMO pump speed), and the presence of continuous renal replacement therapy (CRRT).

Ticagrelor (Brilinta; AstraZeneca, Cambridge, UK) was administered as a 180 mg loading dose (LD) followed by a 90 mg maintenance dose (MD) every 12 h. Paired PK sampling during ON-ECMO (≥ 24 h after initiation) and OFF-ECMO (after weaning) was planned for each patient at pre-dose and 1, 2, 3, 6, 8, and 12 h after ticagrelor administration, and sampling times were recorded. However, not all patients contributed both occasions; therefore, all available data were included in the population PK analysis with ECMO status coded per occasion. All blood samples were collected from an indwelling arterial catheter (A-line) placed as part of routine clinical management.

Blood samples were collected in ethylenediaminetetraacetic acid-coated tubes, centrifuged immediately at 1500 × *g* for 10 min at 4°C, and stored at −80°C until analysis. Plasma concentrations of ticagrelor and AR-C124910XX were quantified using a previously validated liquid chromatography–tandem mass spectrometry method.[20]

Statistical analysis

Paired comparisons of continuous variables between the ON- and OFF-ECMO phases within each patient were performed using the Wilcoxon signed-rank test. A two-sided P value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 4.4.0 (http://www.r-project.org).

Population PK modeling

The population PK model was developed using the first-order conditional estimation method with interaction in NONMEM version 7.4 (ICON Development, Ellicott City, MD, USA). Perl-speaks-NONMEM toolkit, Pirana version 2.9.7 (Certara, Princeton, NJ, USA), and Xpose 4 package version 4.0 (https://xpose.sourceforge.net) in R version 4.4.0 (http://www.r-project.org) were used for data evaluation and visualization. Appendix S1 describes the structural model equations and parameter estimation strategy, while Appendix S2 summarizes the NONMEM control file and simulation structure.

Ticagrelor and AR-C124910XX concentrations were analyzed using a simultaneous parent–metabolite population PK approach. One- and two-compartment disposition models with first-order absorption were compared using objective function value (OFV), diagnostic plots, and parameter plausibility. F denotes absolute bioavailability; therefore, CL/F, Vd/F, CLM/F, and VM/F are apparent parameters. In the parent–metabolite model, CL/F denotes the elimination clearance of ticagrelor, CLM/F represents the elimination clearance of AR-C124910XX from the metabolite compartment, and Vd/F and VM/F denote the Vd for the parent and metabolite, respectively. Interindividual variability (IIV) was modeled exponentially and included on CL/F, Vd/F, and CLM/F.[21]

Residual variability was evaluated using additive, proportional, and combined error models. Based on preliminary model assessment, the proportional component was negligible and did not meaningfully improve model diagnostics; therefore, an additive error model was selected for both parent and metabolite. To support numerical stability, residual error parameters were fixed to the preliminary estimates, with residual variance fixed at 0.1.

The absorption rate constant (Ka) and the fraction of ticagrelor converted to AR-C124910XX (FMET) were fixed due to identifiability limitations in this VA-ECMO dataset, including limited absorption-phase sampling.[22] When Ka and/or FMET were estimated freely, the model showed unstable estimation and poor precision, indicating lack of reliable identifiability. Therefore, Ka was fixed at 0.533 h^{-1} based on a preliminary base model estimation, and FMET was fixed at 0.224 as informed by published ticagrelor population PK models.[23,24]

The following demographic and laboratory covariates were tested: continuous covariates (height, weight, TTSE, DURA, ECMO flow rate, ECMO pump speed, BUN, SCR, UA, TP, ALB, and TB) and categorical covariates (sex [male = 0, female = 1], ECMO [ON-ECMO = 1, OFF-ECMO = 0], smoking [smoking = 1, nonsmoking = 0], and CRRT [presence = 1, absence = 0]). Potential covariates were evaluated using visual inspection, generalized additive models, and were formally selected through stepwise forward inclusion (change in OFV [ΔOFV] > 3.84; $P < 0.05$) followed by backward elimination (ΔOFV > 6.63; $P < 0.01$).[25] Continuous covariates were evaluated using linear, proportional, power, or exponential equations, centering on their median values. Categorical covariates were evaluated using proportional, power, or exponential equations. The final covariate model was selected based on statistical significance and clinical plausibility.

All clearance and volume parameters are reported as apparent values because absolute bioavailability was not estimated.

Final model validation

Model validity was evaluated through a visual inspection of the goodness-of-fit plots (observed concentrations vs. population prediction [PRED] or individual predictions [IPRED] and conditional weighted residuals [CWRES] vs. PRED or time),[22] nonparametric bootstrap resampling method ($n = 5{,}000$), and prediction-corrected visual predictive check (pcVPC; $n = 1{,}000$) for both ticagrelor and AR-C124910XX. The pcVPCs were stratified by ECMO status and assessed by comparing the observed 10th, 50th, and 90th percentiles with the corresponding prediction-corrected simulations percentiles and their confidence intervals.

Sensitivity analysis for fixed parameters

A fixed-parameter sensitivity analysis was performed for Ka and FMET by fixing each parameter to alternative plausible values (including a literature-based Ka), while keeping all other model structures and estimation settings identical to the final model. For each fixed-parameter scenario, the remaining parameters were re-estimated using FOCE-I. Model fit and numerical stability were summarized using OFV, ΔOFV, and minimization/covariance-step status. When minimization terminated or the covariance step was aborted, standard errors were not available and were reported as NA. Detailed results are provided in Appendix S3.

Target concentration range definition

Because no ECMO-specific exposure–response targets for ticagrelor have been established, the target concentration range was defined using mechanistically anchored pharmacodynamic (PD) cutoffs reflecting plateaus in antiplatelet efficacy and inflection points in bleeding risk.

The lower bound (180 ng/mL) was based on the plasma concentration associated with ~ 80% platelet inhibition (~ 344 nmol/L), corresponding to the onset of near-maximal P2Y12 receptor blockade and the established efficacy plateau observed in prior exposure–response analyses. Selection of this threshold was therefore intended to ensure pharmacologic efficacy rather than to reflect a population-specific clinical reference.[23] The upper bound (360 ng/mL) was derived from a logistic regression model linking ticagrelor minimum concentration (Cmin) to major bleeding risk (area under the receiver operating characteristic curve = 0.65; 95% confidence interval (CIs), 0.595–0.700; $P < 0.001$), in which bleeding probability increased steeply beyond a concentration of 363.3 ng/mL. This cutoff was interpreted as a PD risk inflection point rather than a strict safety threshold.[26] In the absence of validated ECMO-specific pharmacodynamic

Table 1 Patient characteristics

N=20	ON-ECMO	OFF-ECMO	*P*
Age, years	59 (36–88)		
Male, *n*	18		
Body weight, kg	70.8 (58–110)	70.95 (58–110)	
Body mass index, kg/m^2	25.13 (20.65–35.92)	24.85 (20.65–35.92)	
STEMI/NSTEMI	19/1		
PCI	19		
Cardiac arrest	15/5		
Blood chemistry during ECMO, serum levels			
BUN[a], mg/dL	20.8 (9–40.9)	43.8 (12.5–66.6)	0.03
SCR[a], mg/dL	1.30 (0.79–4.89)	1.72 (1.16–4.38)	0.03
Uric acid[a], mg/dL	3.05 (1.6–9.3)	3.1 (1.7–6.2)	0.09
Aspartate aminotransferase, IU/L	155 (56–1,430)	63.5 (11–712)	0.06
Alanine aminotransferase, IU/L	83 (27,808)	59.5 (17–229)	0.89
Total protein, g/dL	4.9 (4.2–6.1)	5.55 (4.8–6.4)	0.02
Albumin, g/dL	2.9 (2.5–3.6)	2.95 (2.4–3.4)	1
Total bilirubin, mg/dL	2.1 (0.9–6.3)	1.4 (0.4–24.2)	0.67
Use of CRRT, *n*	5	6	
Duration of VA-ECMO, days	5.87 (1.82–16.26)		

Note: Data are presented as median (range) or number of patients. *P*-values were calculated using the Wilcoxon signed-rank test to compare ON- and OFF-ECMO phases within the same patient. Data were obtained from 20 patients, with 127 ON-ECMO and 98 OFF-ECMO plasma concentration observations.Abbreviations: BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SCR, serum creatinine; STEMI, ST-elevation myocardial infarction; VA-ECMO, veno-arterial extracorporeal membrane oxygenation. [a]BUN, SCR, and uric acid levels were not evaluated for patients on CRRT.

targets, this efficacy–risk–anchored concentration window was used as a translational framework to support model-informed dosing simulations. Because the source exposure–response models incorporated the effects of the active metabolite, dose simulations were performed using parent ticagrelor concentrations as a practical surrogate for overall antiplatelet activity.

Monte Carlo simulations

Monte Carlo simulations (n = 1,000) using final model parameters evaluated ticagrelor dosing during VA-ECMO. LDs of 90, 120, 135, and 180 mg and MDs of 45, 60, and 90 mg were tested at 12-, 24-, and 48-h intervals, starting 12 h after the LD. After weaning the patients off VA-ECMO, the MD was fixed at 90 mg every 12 h. Clinical scenarios included the following: (1) 6-day plan – ECMO flow 3.4 L/min for 3 days, reduced by 0.3 L/min every 6 h over 2 days, then 1 L/min for the final 24 h, and (2) 9-day plan––flow 3.4 L/min for 5–6 days, reduced by 0.2–0.3 L/min every 6 h for 2–3 days, then 1 L/min on the last day. Simulation outputs were summarized using the median population prediction and the 10th–90th percentiles to describe variability across individuals. As described above, we selected the dosage based on the minimum concentration of 180–360 ng/mL at steady state.

RESULTS

Patient characteristics

A total of 20 patients were enrolled from October 2015 to April 2018 (Table 1). The median age was 59 (range, 36–88) years with 18 men and 2 women. Median body weight was 70.2 (58–110) kg and median body mass index was 25.1 (20.7–35.9) kg/m^2. All the patients received blood transfusions, 18 received albumin, and six underwent CRRT while on VA-ECMO. The median duration of VA-ECMO was 5.87 (1.82–16.26) days. Overall, 127 and 98 blood samples were obtained from 19 patients ON-ECMO and 13 patients OFF-ECMO, respectively.

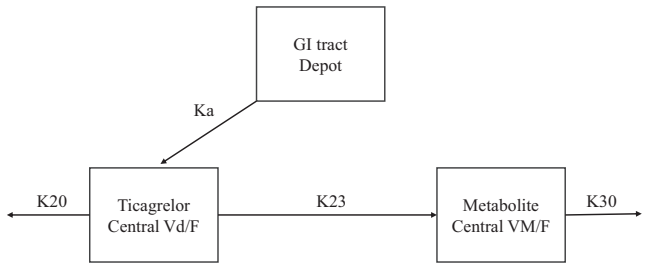

Figure 1 Structure of parent-metabolite model. K20=(1−FMET)·(CL/F)/(Vd/F), K23=FMET·(CL/F)/(Vd/F), K30=(CLM/F)/(VM/F). FMET, fraction of ticagrelor converted to metabolite; GI, gastrointestinal; Ka, absorption rate constant; K20, ticagrelor elimination rate constant; K23, metabolite formation rate constant; K30, metabolite elimination rate constant; Vd/F, volume of distribution of ticagrelor; VM/F, volume of distribution of metabolite. Since (CL/F)/(Vd/F)=CL/Vd, the rate constant K20 and K23 are independent of bioavailability (F).

Population PK modeling and evaluation

The PK of ticagrelor and its active metabolite, AR-C124910XX, where best described by a one-compartment parent-metabolite model (Figure 1),[27] in which ticagrelor enters the parent compartment and is eliminated via CL/F, while AR-C124910XX is described by a metabolite compartment with its own elimination

Table 2 Parameters of final ticagrelor model

Parameters	Population estimations (%RSE)[a]	Bootstrap median	Bootstrap 95% CI
Fixed effects			
$\theta_{CL/F}$	12.2 (16.7)	12.01	8.99–16.24
$\theta_{Vd/F}$	157 (17.4)	152.93	101.04–291.14
$\theta_{CLM/F}$	8.8 (10.7)	8.83	7.27–10.76
$\theta_{VM/F}$	29.5 (42.7)	28.86	12.63–102.22
θ_{Ka}	0.533 FIX		
θ_{FMET}	0.224 FIX		
θ_{ECMO} on CL/F	0.35 (6.5)	0.356	0.302–0.433
θ_{ECMO} on Vd/F	2.74 (34.5)	2.82	1.28–5.30
$\theta_{ECMO\ flow\ rate}$ on Vd/F	0.518 (32)	0.526	0.248–0.839
Random effects			
Interindividual variability [%CV][b]			
$\omega^2_{CL/F}$	0.441 (34.7) [74.4]	0.420	0.188–0.684
$\omega^2_{Vd/F}$	0.661 (34) [96.8]	0.624	0.310–1.06
$\omega^2_{CLM/F}$	0.156 (47.74) [41.1]	0.144	0.051–0.315
Residual variability[c]			
σ_{ADD}	1.65 FIX		
σ_{ADDM}	0.2 FIX		

Note: Population pharmacokinetic parameter estimates were based on 20 patients (127 ON-ECMO and 98 OFF-ECMO observations). All clearance and volume parameters are reported as apparent values (CL/F, Vd/F, CLM/F, and VM/F) because absolute bioavailability was not estimated.Abbreviations: ADD, additive residual error (parent); ADDM, additive residual error (metabolite); CI, confidence interval; CL/F, apparent ticagrelor clearance; CLM/F, apparent metabolite clearance; ECMO, extracorporeal membrane oxygenation; FMET, metabolic conversion fraction; Ka, absorption rate constant; RSE, relative standard error; SD, standard deviation; Vd/F, apparent volume of distribution of ticagrelor; VM/F, apparent Vd of metabolite; W, additive error parameter. [a]%RSE=(standard error/parameter estimate)×100. [b]%CV=sqrt(exp(ω^2)−1)×100. [c]Residual variance was fixed at 0.1; therefore, residual SD=sqrt(0.1)×W.

clearance (CLM/F). IIV included CL/F, Vd/F, and CLM/F. Residual variability was described by an additive error model with fixed parameters (Table 2). ECMO status and flow rate significantly influenced ticagrelor CL/F and Vd/F (model details in Appendix S1).

The final PK model of ticagrelor was as follows:

- $CL/F\ (L/h) = 12.2 \times (0.35)^{ECMO}$, where ON-ECMO = 1 and OFF-ECMO = 0
- $Vd/F\ (L) = 157 \times 0.518^{(ECMO\ flow\ rate/3)} \times 2.74^{ECMO}$, where ON-ECMO = 1 and OFF-ECMO = 0
- $CLM/F\ (L/h) = 8.8$
- $VM/F\ (L) = 29.5$
- $Ka\ (h^{-1}) = 0.533$
- $FMET = 0.224$

The population CL/Fs ON- and OFF-ECMO were 4.27 and 12.2 L/h, respectively. At an ECMO flow rate of 3 L/min, Vd/F was 222.8 L ON- and 81.3 L OFF-ECMO. Reducing the ECMO flow rate to 1 L/min increased the Vd/F to 345.5 L.

The parameters of the final ticagrelor model are described in Table 2. IIV, expressed as the coefficient of variation (%CV), was higher than that reported in non-ECMO populations.[23] The goodness-of-fit plots for the final models are shown in Figure 2. The CWRES were generally centered around zero, although some positive skew was observed. The stratified pcVPC for ticagrelor and AR-C124910XX (Figure S1) showed that the observed prediction-corrected percentiles were generally captured by the corresponding simulation-based confidence intervals, supporting adequate predictive performance.

Simulation and dose optimization

Figure 3 and Figure S2 show the 6-day plan results, presenting the median PRED together with the 80% prediction interval (10th–90th percentiles of IPRED) from the Monte Carlo simulations. All Cmin were within the therapeutic range with LDs of 120 or 135 mg, followed by MDs of 60 or 90 mg once daily. When the 9-day plan was applied, an MD of 60 mg once daily met the target reference range across all LDs, whereas 90 mg failed in some patients with prolonged high ECMO flow (Figure S4). Based on these simulations, an LD of 120 or 135 mg followed by an MD of 60 mg once daily throughout the course of VA-ECMO most consistently maintained predicted trough concentrations within the prespecified target range across all scenarios, whereas a 90 mg once daily MD frequently exceeded the upper bound. These findings support the need for further evaluation of reduced once-daily dosing during VA-ECMO.

DISCUSSION

This study evaluated a population PK model for ticagrelor and its active metabolite during VA-ECMO, and included Monte Carlo simulations to identify optimal dosing. Maintaining adequate therapeutic concentrations of antiplatelet drugs is crucial in the treatment of ACS. Although cardiogenic shock due to ACS is a common indication for ECMO in adults,[14,15,28] antiplatelet management in this setting remains challenging because substantial risks of both thrombosis and bleeding exist and ticagrelor dosing is still largely extrapolated from non-ECMO populations. To the best of our knowledge, this is the first study to investigate ticagrelor dose optimization in critically ill patients with ACS on VA-ECMO. Our model provides an initial quantitative framework to support dose individualization during VA-ECMO, a setting in which thrombotic and bleeding risks coexist and ticagrelor dosing remains largely extrapolated from non-ECMO populations.

Our simulations indicated that lower than standard ticagrelor doses may provide adequate efficacy in patients on VA-ECMO, reflecting reduced CL/F and increased Vd/F. Regimens with a 120–135 mg LD and 60 mg once daily MD maintained predicted trough concentrations within the prespecified target range more consistently than standard dosing. These findings should be prospectively validated in larger PK-PD studies before clinical implementation.

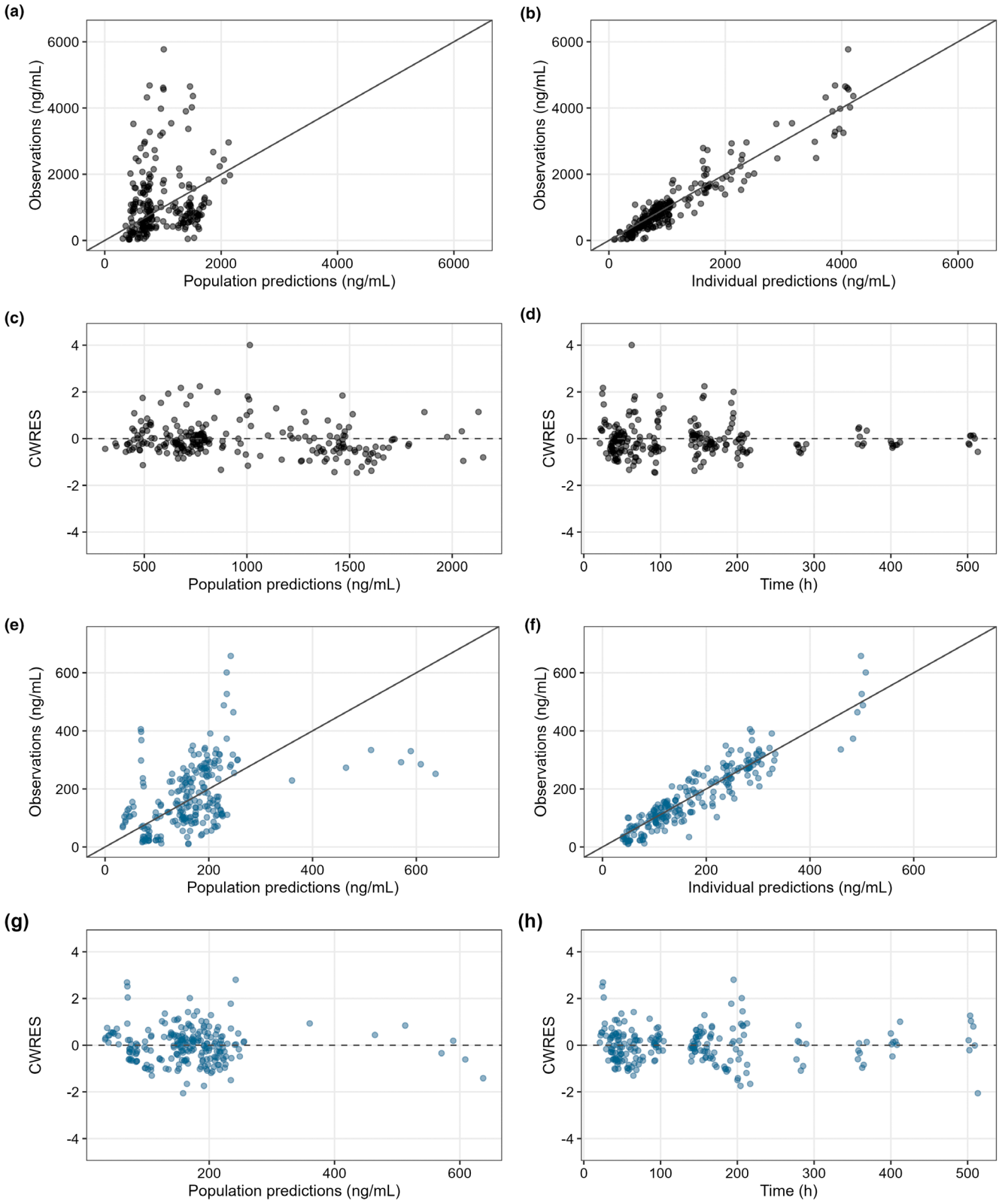

Figure 2 Goodness-of-fit plots for the final population pharmacokinetic model of ticagrelor and AR-C124910XX. Black circles (a–d) represent ticagrelor, and blue circles (e–h) represent the active metabolite AR-C124910XX. Observed concentrations are shown versus population predictions (a, e) and individual predictions (b, f). Conditional weighted residuals (CWRES) are plotted versus population predictions (c, g) and time (d, h). Solid lines indicate the line of identity (y=x), and dashed lines indicate the zero reference lines.

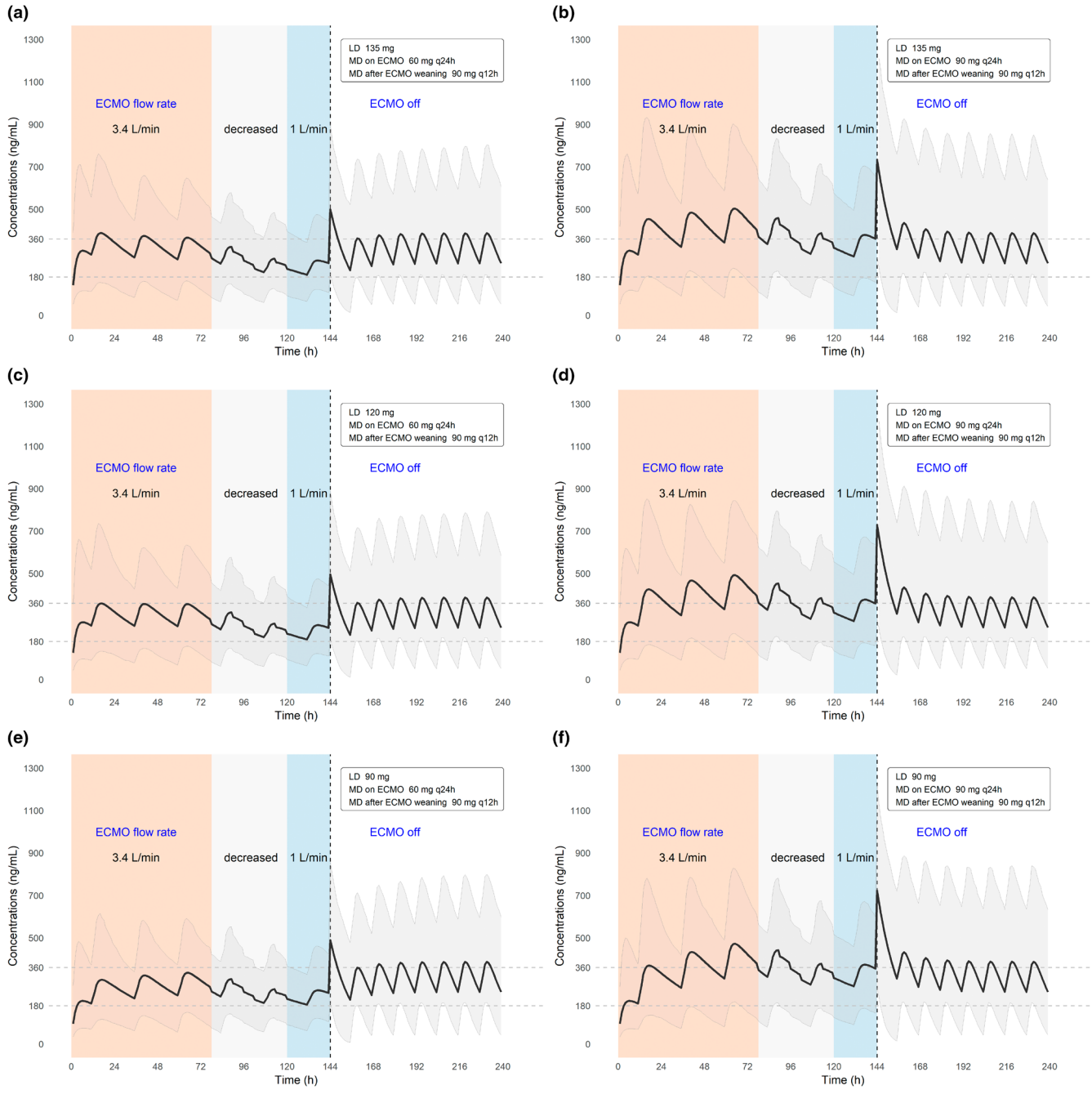

Figure 3 Monte Carlo simulation results applying 6-day ECMO plan. Panels (a–f) show simulations under six regimens during ECMO: (1) LD 135 mg and MD 60 mg every 24 h (q24h); (b) LD 135 mg and MD 90 mg q24h; (c) LD 120 mg and MD 60 mg q24h; (d) LD 120 mg and MD 90 mg q24h; (e) LD 90 mg and MD 60 mg q24h; and (f) LD 90 mg and MD 90 mg q24h. After ECMO weaning, a standard dose of 90 mg q12h was used. The solid black line represents the typical population prediction, and the gray shaded area indicates the 80% prediction interval (10th–90th percentiles of individual predictions) across 1000 simulated patients. Pink area indicated an ECMO flow rate of 3.4 L/min for 3 days, followed by a w-day tapering period (first white area). The blue area indicates 1 L/min for 1 day, and the second white area indicates ECMO off. Gray dashed lines indicate the target reference range. ECMO, extracorporeal membrane oxygenation; LD, loading dose; MD, maintenance dose; q24h, every 24 hours; q12h, every 12 hours.

Patients on VA-ECMO require systemic anticoagulation—typically unfractionated heparin[29]—and are exposed to non-pulsatile flow and artificial surfaces, which increase bleeding risk.[30–32] Dual antiplatelet therapy with ticagrelor may further augment this risk. Because platelet function and clinical outcome data were not collected in this study, direct links between model-predicted exposure and clinical efficacy or safety could not be established. Nevertheless, the present model and simulations provide a quantitative basis for dose individualization during VA-ECMO. The proposed regimens, however, should be tested in future PK-PD studies to further evaluate our findings.

We have described herein the PK of ticagrelor using a one-compartment parent-metabolite model. VA-ECMO significantly affected the CL/F and Vd/F of ticagrelor, with the ECMO flow rate specifically affecting Vd/F. Although previous studies have developed separate PK models for ticagrelor and AR-C124910XX,[23,24,33–35] to the best of our knowledge, this is the first to combine both using a parent-metabolite model. Covariates such as smoking, body weight, sex, and CYP3A modulators influenced ticagrelor pharmacokinetics among individuals not on ECMO,[33,34] but did not improve our model in critically ill patients on VA-ECMO.

The decreased CL/F in patients receiving VA-ECMO was a noteworthy observation. Most patients received VA-ECMO in the treatment of severe cardiogenic shock, indicating significantly reduced cardiac output and subsequent hypoperfusion of end organs, including the liver and kidneys.[36–38] As ticagrelor is metabolized primarily hepatically with minimal renal excretion,[39] impaired hepatic function may decrease CL/F.[4,6] Because ticagrelor is highly protein-bound and has been described as a low hepatic extraction drug,[39,40] changes in intrinsic metabolic capacity rather than hepatic blood flow alone may underlie the observed PK differences during VA-ECMO. In addition, non-pulsatile ECMO flow may reduce the renal elimination of drugs,[4] and sequestration within the ECMO circuit due to high lipophilicity and protein binding (99% affinity)[16,41] may contribute.[4,10,42]

Another finding from this study was increased Vd/F in the ON-ECMO group, likely reflecting VA-ECMO-related factors and critical illness. Vasodilation and fluid retention, in conjunction with resuscitation fluids, transfusions, albumin, and priming solutions, promote hemodilution and increase ticagrelor Vd/F.[4,43] All 20 patients in this study received blood transfusions, and 18 received albumin. Drug sequestration in the ECMO circuit and reduced plasma protein levels from liver dysfunction may have further altered the free fraction of ticagrelor and systemic exposure.[4,9,42] However, because no invitro circuit extraction experiment was performed, ECMO-related sequestration cannot be fully separated from critical illness-associated physiological effects.

This study had some limitations that should be discussed. The sample size was small and all patients were enrolled at a single center, limiting the precision of the population PK parameter estimates and the generalizability of our findings. In particular, the higher variability observed for AR-C124910XX suggests that metabolite kinetics were less precisely estimated. Substantial IIV in the pcVPCs, together with a higher estimated IIV (%CV) in the ECMO population than in the non-ECMO population,[23] reflects the marked heterogeneity of patients on VA-ECMO. Fixed-parameter sensitivity analyses showed stable parent parameter estimates across plausible FMET values, while metabolite parameters varied compensatorily with an essentially unchanged metabolite elimination rate (CLM/VM), supporting robustness of the parent exposure–driven conclusions (Appendix S3). Overall model performance was supported by goodness-of-fit diagnostics and pcVPCs, although uncertainty was higher for AR-C124910XX (Figure S1). External validation in larger cohorts is needed.

Because no *in vitro* ECMO circuit extraction experiments were performed, the observed PK differences between ON-ECMO and OFF-ECMO occasions may reflect a combination of circuit-related effects (e.g., sequestration/hemodilution) and evolving patient physiology during recovery. In addition, ECMO flow rate may be confounded by disease severity, and circuit extraction may be time- and flow-dependent; therefore, any apparent flow rate-dependent effects should be interpreted cautiously and considered exploratory.

Furthermore, we did not assess platelet function or systematically collect thrombotic or bleeding outcomes, so the model links ticagrelor exposure only to an external PK/PD target and not to clinical events. The target range derived from previous non-ECMO cohorts also may not fully capture the altered hemostatic balance that occurs during VA-ECMO; therefore, the appropriateness of this range in this population requires further validation, and concentrations within this range should be interpreted in conjunction with individual bleeding and thrombotic risk.

Finally, although we evaluated several clinical and ECMO-related covariates, other potentially important health-related covariates may not have been fully captured or could not be reliably assessed in this cohort because of the limited sample size, which suggests that ticagrelor dosing should still be individualized using both model predictions and clinical judgment and that future studies incorporating a broader set of covariates will be needed to improve predictive performance.

Despite these limitations, this study is, to the best of our knowledge, the first to characterize the population PK of ticagrelor and its active metabolite during VA-ECMO and to explore dosing strategies using model-informed simulations under varying ECMO flow conditions. In these simulations, regimens with a 120–135 mg LD followed by a 60 mg once daily MD maintained predicted trough concentrations within the prespecified target range more consistently than standard dosing. These regimens may help inform dosing hypothesis for patients with ACS on VA-ECMO, particularly those with a high bleeding risk. Overall, these findings suggest that standard ticagrelor dosing cannot be assumed during VA-ECMO, and larger outcome-linked PK-PD studies are warranted to define safe and effective antiplatelet strategies in this population.

In conclusion, we developed a parent-metabolite population PK model for ticagrelor and AR-C124910XX in patients undergoing VA-ECMO and identified ECMO status and flow rate as important determinants of ticagrelor disposition. These findings provide a quantitative basis for dose individualization in this specific population and should be further evaluated in larger PK-PD and clinical outcome studies.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

S.K., J.W., and M.J.C. wrote the manuscript; S.K., K.L.M., S.Y., J.H., D.K., B.H.J., J.W., and M.J.C. designed the research; S.K., K.L.M., S.Y., J.H., D.K., B.H.J., S.U.C., S.K.B., J.W., and M.J.C. performed the research; S.K. and K.L.M. analyzed the data.

DATA AVAILABILITY STATEMENT

The data used in this study are not publicly available to ensure the privacy of individuals that participated in the study. Research data can only be used for research purposes and access to the data requires special approval. The data underlying this article are available upon reasonable request to the corresponding author.

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