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Article

A Digital Twin of the Angiotensin II Receptor Blocker Losartan: Physiologically Based Modeling of Blood Pressure Regulation

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Abstract

Losartan, a commonly prescribed angiotensin II receptor blocker (ARB) used to treat hypertension and heart failure, shows significant variability in pharmacokinetics (PK) and pharmacodynamics (PD) among individuals. In this study, we developed a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model of losartan and its active metabolite, E3174, using curated data from 24 clinical trials. The model, implemented in SBML, mechanistically describes the processes of absorption, hepatic metabolism, renal excretion, and pharmacodynamic regulation via the renin–angiotensin–aldosterone system (RAAS). Simulation studies examined the effects of dose, hepatic and renal impairment, and genetic polymorphisms in CYP2C9 and ABCB1 on the model. The model successfully reproduced key PK/PD observations, including dose-dependent receptor blockade, attenuated responses with hepatic impairment, modest enhancement with renal impairment, and substantial variability in E3174 formation dependent on CYP2C9; the effects of ABCB1 were minimal. This mechanistic digital twin framework provides a quantitative basis for understanding variability in losartan therapy and supports its application in individualized dosing strategies.

Keywords: Losartan; Angiotensin II Receptor Blocker; ARB; PBPK/PD modeling; Pharmacokinetics; Pharmacodynamics; SBML

1. Introduction

Hypertension, defined as blood pressure of 130 mmHg or higher and/or a diastolic blood pressure of 80 mmHg or higher, is a major global health challenge and leading risk factor for cardiovascular disease, stroke, and kidney failure [1–3]. In 2019, over 1.2 billion people worldwide were affected, with prevalence exceeding 50% in some regions [2]. Despite its silent clinical course, hypertension contributes to over 8 million deaths annually [3]. Risk factors include age, genetics, obesity, inactivity, and unhealthy diet [1]. While treatment options exist, improved prevention and personalized therapies remain essential.

The renin-angiotensin-aldosterone system (RAAS) regulates blood pressure and fluid balance. Renin release from the kidney cleaves angiotensinogen to angiotensin I, which is converted by the angiotensin converting enzyme (ACE) into angiotensin II [4]. Angiotensin II raises blood pressure via vasoconstriction, stimulation of aldosterone and vasopressin release, enhanced sodium reabsorption, and increased sympathetic tone [5]. Dysregulation of the RAAS underlies hypertension, heart failure, and kidney disease.

Pharmacological treatments target RAAS at multiple points. Beta-blockers lower renin, direct renin inhibitors (e.g., aliskiren) block its activity, ACE inhibitors (e.g., ramipril) prevent angiotensin II formation, and angiotensin II receptor blockers (ARBs) (e.g., losartan) selectively antagonize AT1

receptors [5–8]. ARBs offer high specificity by blocking receptor-mediated effects of angiotensin II without interfering with its synthesis. Other antihypertensive drug classes include diuretics and calcium channel blockers [9,10].

Losartan, the first ARB approved in 1995, is widely prescribed for hypertension and related complications [11,12]. By competitively blocking AT1 receptors, it reduces vasoconstriction, aldosterone secretion, and water retention. Its major active metabolite, E3174, is generated through CYP2C9 mediated conversion and 10–40 times more potent [13], though losartan itself remains an effective antagonist. Both compounds contribute to clinical efficacy. Losartan is well tolerated, with dizziness and mild respiratory symptoms as the most common side effects [12]. It is available as monotherapy or combined with hydrochlorothiazide for greater blood pressure reduction [14]. Standard dosing ranges from 25–100 mg/day. Like other ARBs, it is contraindicated in pregnancy [11].

Losartan shows rapid oral absorption, with peak plasma levels after 1–2 h and bioavailability of about 33% due to first-pass metabolism [13,15]. E3174 peaks later (3–4 h) and has 4–8-fold higher systemic exposure [13,16]. Both compounds bind strongly to plasma proteins and are eliminated via hepatic metabolism and renal/fecal excretion, with terminal half-lives of 2 h (losartan) and 4–6 h (E3174) [17,18]. Only small fractions are excreted unchanged renally [19]. Minor metabolites such as L158 reflect additional metabolic pathways [18,20].

Pharmacodynamically, losartan lowers blood pressure by blocking AT1 receptors, thereby reducing aldosterone secretion [21–23]. AT1 blockade also increases renin and angiotensin levels due to loss of feedback control [24,25]. Enhanced stimulation of AT2 receptors may further contribute to vasodilation [26].

Liver cirrhosis reduces losartan clearance by about 50% and doubles bioavailability, leading to higher plasma levels, though E3174 exposure increases only modestly [11,27]. Renal impairment decreases clearance of losartan and E3174 but generally does not elevate E3174 levels due to compensatory mechanisms [19,28,29]. Neither compound is dialyzable, and dose adjustments are mainly required in hepatic dysfunction [30].

Drug response varies due to genetic polymorphisms in ABCB1 and CYP2C9 genes. Variants of ABCB1, a gene encoding for a drug efflux transporter also known as P-glycoprotein or MDR1, influence losartan absorption and blood pressure response, though findings are inconsistent [31–33]. CYP2C9 polymorphisms (*2, *3, *13) reduce metabolism to E3174, increasing losartan exposure and diminishing therapeutic effect [13,34–37]. The frequency of these alleles varies by population [38–40].

Physiologically-based pharmacokinetic/ pharmacodynamic (PBPK/PD) models integrate ADME processes (absorption, distribution, metabolism and elimination) with drug effects using differential equations [41]. They allow simulation of dosing regimens, organ dysfunction, and genetic variability on drug behavior. In this work, a PBPK/PD model of losartan was developed to investigate dose-dependent PK/PD effects, the influence of hepatic and renal impairment and the impact of ABCB1 and CYP2C9 variants. The aim is to clarify sources of variability in losartan response and support individualized therapy.

2. Materials and Methods

2.1. Systematic Literature Research

A systematic literature search was performed in PubMed and PKPDAI [42] on 27 August 2024 using the terms losartan AND pharmacokinetics. Eligible studies included human clinical trials with PK/PD data in healthy volunteers, hepatic/renal impairment, or CYP2C9 genotypes. Excluded were animal studies, pediatric/ single-patient reports, reviews, computational models, cocktail or combination designs, and PD-only studies. Where data were redundant, representative studies were selected. Additional *in vitro* reports were included to derive kinetic parameters.

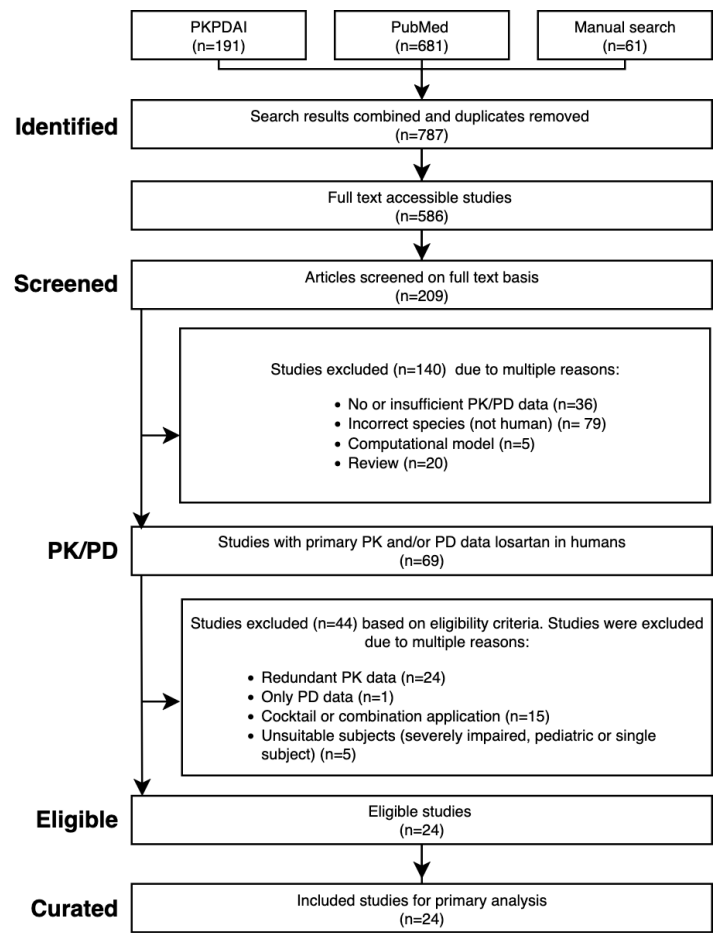


Figure 1. PRISMA flow diagram of the literature search and study selection process.

2.2. Data Curation

Relevant study data were curated into PK-DB [43]. Extracted metadata included group and individual characteristics (age, sex, genotype, comorbidities), interventions (dose, route, regimen), and outcomes (concentration-time profiles of losartan and metabolites, RAAS biomarkers, blood pressure, heart rate). Digitization of graphical data was performed using WebPlotDigitizer [44]. Data were organized according to PK-DB standards into groups, individuals, interventions, and time courses, providing the heterogeneous dataset used for modeling and validation.

2.3. Computational Model

A physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model was built in the Systems Biology Markup Language (SBML) [45,46] using sbmlutils [47], visualized using cysbml [48], simulated with sbmlsim [49] based on libroadrunner [50,51], and shared under CC-BY 4.0 at Zenodo (v0.7.1) [52]. The model consists of submodels for intestine, liver, kidney, and RAAS, connected by systemic circulation. Hepatic impairment was implemented as progressive cirrhosis [53,54], aligned with Child-Pugh classes [55,56]. Renal impairment was modeled as reduced clearance based on glomerular filtration rate following KDIGO guidelines [57,58]. CYP2C9 genetic variability was incorporated using allele-specific activity scaling [59–61], and ABCB1 activity was adjusted according to published polymorphism data [62,63].

2.4. Parameter Optimization

Model parameters were estimated by minimizing weighted residuals between clinical data and simulations. The cost function was defined as

$$F(\vec{p}) = 0.5 \sum_{i,k} (w_{i,k} \cdot r_{i,k}(\vec{p}))^2,$$

with weights $w_{i,k} = n_k / \sigma_{i,k}$ based on study size and measurement error. One hundred optimization runs with varying initial conditions were performed. Fitting proceeded in two stages: first pharmacokinetic, then pharmacodynamic parameters. Independent datasets including multiple dosing and impairment scenarios were used for validation.

2.5. Pharmacokinetic and Pharmacodynamic Parameters

Pharmacokinetic parameters for losartan, E3174, and L158 were derived using non-compartmental methods. The elimination rate (k_{el}) was estimated from log-linear regression of the terminal phase. The area under the concentration-time curve (AUC) was computed by trapezoidal rule and extrapolation. Apparent clearance (Cl/F) and volume of distribution (V_d/F) were derived from $Cl/F = k_{el} \cdot V_d$ and $V_d/F = D/(AUC_{\infty} \cdot k_{el})$, where D is dose. Pharmacodynamic outputs (renin, angiotensin, aldosterone, blood pressure) were summarized by maximal and minimal values.

3. Results

3.1. Losartan Database

An open database containing pharmacokinetic and pharmacodynamic data of losartan from 24 clinical studies was compiled, covering a range of dosing regimens, physiological conditions and different genotypes (Table 1). This dataset served as the basis for developing the losartan PBPK/PD model.

Table 1. Summary of studies for modeling. Overview of study identifiers, PK-DB IDs, administered substance and administration route, dosing regimens, doses [mg], and subject characteristics, including health status, renal functional impairment (*RFI*), hepatic functional impairment (*HFI*), and the studied genotypes (*CYP2C9*, *ABCB1*).

Study	PK-DB	Substance	Route	Dosing	Dose [mg]	Healthy	RFI	HFI	CYP2C9	ABCB1
Bae2011 [64]	PKDB00895	losartan potassium	po	single	50	✓			✓	
Donzelli2014 [65]	PKDB00953	losartan	po	single	12.5	✓				✓
FDA1995S60 [18]	PKDB00965	C14 losartan, e3174	po/iv, iv	single	100/30, 20	✓				
FDA1995S67 [18]	PKDB00966	losartan, e3174	po/iv, iv	single	50/10, 10			✓		
Fischer2002 [37]	PKDB00894	losartan	po	multi	50	✓			✓	
Han2009a [66]	PKDB00909	losartan potassium	po	single	50	✓			✓	
Huang2021 [67]	PKDB00919	losartan potassium	po	single	50	✓			✓	
Kim2016 [68]	PKDB00896	losartan	po	single	50	✓				✓
Kobayashi2008 [69]	PKDB00920	losartan potassium	po	single	25	✓				
Lee2003b [70]	PKDB00899	losartan potassium	po	single	50	✓				✓
Li2009 [40]	PKDB00912	losartan	po	single	50	✓				✓
Lo1995 [13]	PKDB00922	losartan potassium, e3174	po/iv	single	50, 100/20, 30	✓				
Munaf01992 [71]	PKDB00921	losartan	po	single	40, 80, 120	✓				
Oh2012 [72]	PKDB00054	losartan	po	single	2	✓				
Ohtawa1993 [16]	PKDB00911	losartan	po	single, multi	25, 50, 100, 200	✓				
Puris2019 [73]	PKDB00642	losartan potassium	po	single	12.5					
Sekino2003 [36]	PKDB00961	losartan	po	single	25	✓			✓	
Shin2020 [32]	PKDB00898	losartan potassium	po	single	50	✓				✓
Sica1995 [19]	PKDB00910	losartan	po	multi	100		✓			
Tanaka2014 [74]	PKDB00136	losartan	po	single	50	✓				
Yasar2002a [35]	PKDB00897	losartan	po	single	50	✓			✓	

3.2. Computational Model

A PBPK/PD model of losartan was created that includes key factors that determine intra- and inter-individual variability (Figure 2). The model includes the organs involved in the pharmacokinetics of losartan (gastrointestinal tract, liver, and kidney), connected through the systemic circulation, as well as the main pharmacodynamic outputs of the RAAS (renin, angiotensin I, aldosterone, systolic and diastolic blood pressure). The main patient-specific factors that are known to affect the pharmacokinetics and pharmacodynamics of losartan are included in the model. Specifically, four key factors were included: dose dependency, liver impairment, renal impairment, and genotype variability.

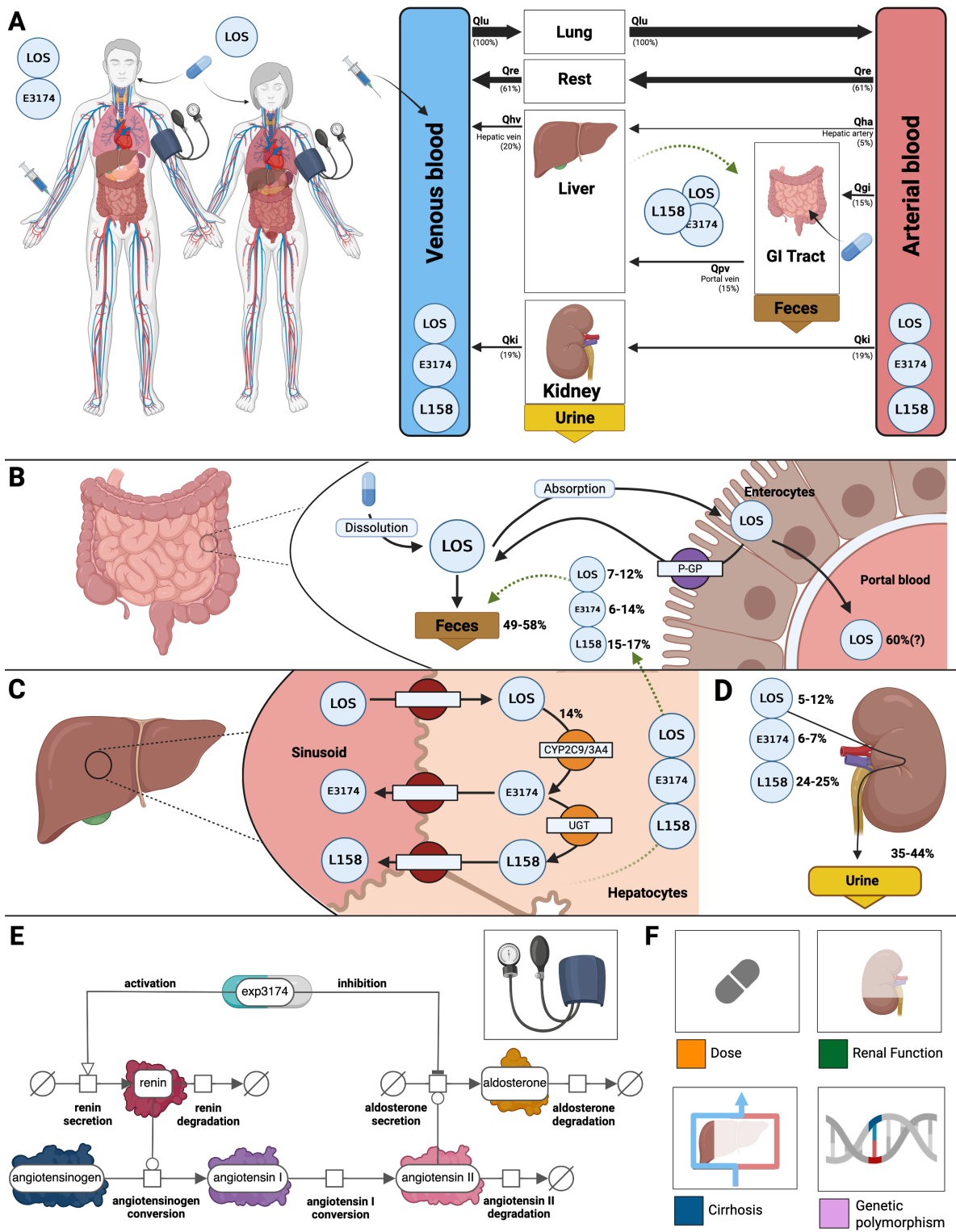


Figure 2. Overview of the physiologically-based model of losartan. (A) Whole body model showing circulation via the arterial and venous blood, with organs (liver, GI tract, kidney) influencing the pharmacokinetics of losartan (LOS). (B) Intestine model illustrating the dissolution and absorption of LOS by enterocytes and the P-glycoprotein mediated efflux back into the intestine. Approximately 49-58% of the dose is excreted as losartan or metabolites (E3174 and L158). (C) Hepatic model depicting the uptake of losartan by hepatocytes and its conversion by cytochrome p450 2C9 and 3A4 (CYP2C9, CYP3A4) to losartan carboxylic acid E3174 (14% of losartan dose) and the following conversion by UDP-glucuronosyltransferase (UGT) to L158. Losartan and its metabolites can also re-enter the intestinal model via enterohepatic circulation (biliary export). (D) Renal model showing excretion of losartan, E3174 and L158 via urine, approximately 5-12%, 6-7% and 24-25%, respectively. (E) Pharmacodynamic model of E3174 acting on the RAAS. (F) Key factors influencing losartan PK and PD profiles accounted for in the model. Illustrations for losartan dosing, hepatic impairment, renal impairment and genetic polymorphisms.

3.3. Dose Dependency

Dose-dependent behavior of the losartan PBPK/PD model was assessed by simulating oral doses between 10 and 100 mg (Figure 3). The model captures the pharmacokinetics of losartan and its active metabolite E3174 in plasma, urine, and feces, as well as the associated pharmacodynamic responses (aldosterone, renin, angiotensin I, and blood pressure). Simulations reproduced key dose-related trends: increasing exposure with dose, a decreasing E3174/losartan ratio at higher doses, nonlinear increases in AUC and C_{max} (particularly for E3174), and dose-dependent prolongation of E3174 half-life. On the pharmacodynamic level, higher doses produced stronger suppression of aldosterone and blood pressure, accompanied by compensatory increases in renin and angiotensin I. These patterns are consistent with findings from published clinical studies (Figure 3 and 4).

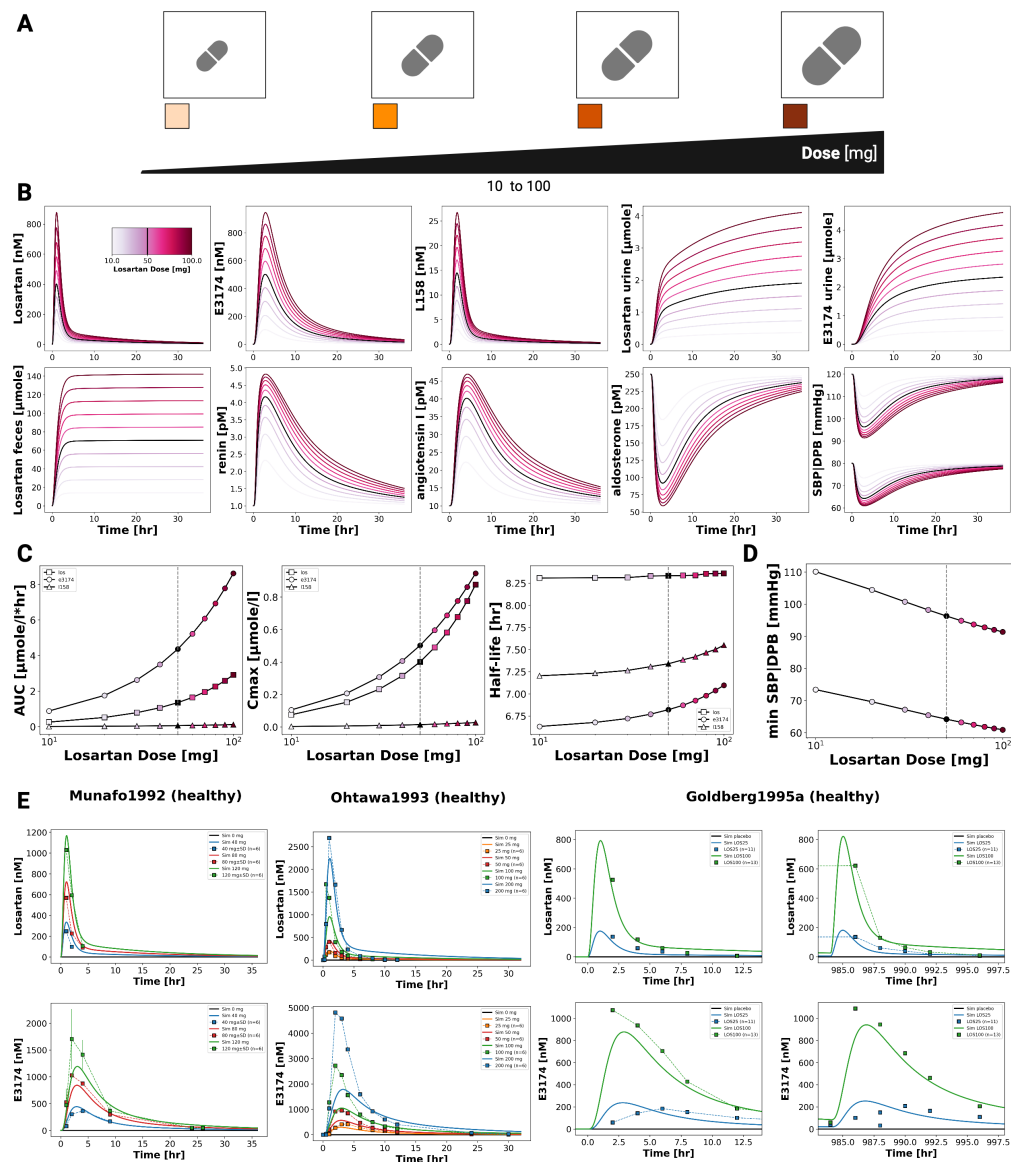


Figure 3. Dose-dependent pharmacokinetics and pharmacodynamics of losartan. (A) Illustration of the losartan dose range (10–100 mg) evaluated in the simulations. (B) Simulated plasma concentrations profiles of losartan, E3174 and L158, urinary excretion profile of losartan and E3174, a fecal excretion profile of losartan as well as simulated RAAS biomarkers (renin, angiotensin I and aldosterone) and blood pressure responses across doses (10–100 mg). Dose intensity is indicated by line color. (C) Dose–response curves for AUC, C_{max} and half-life. (D) Dose dependent maximum or minimum values of systolic blood pressure SBP and diastolic blood pressure DBP. (E) Simulated versus observed losartan pharmacokinetics. Data from [16,71,75].

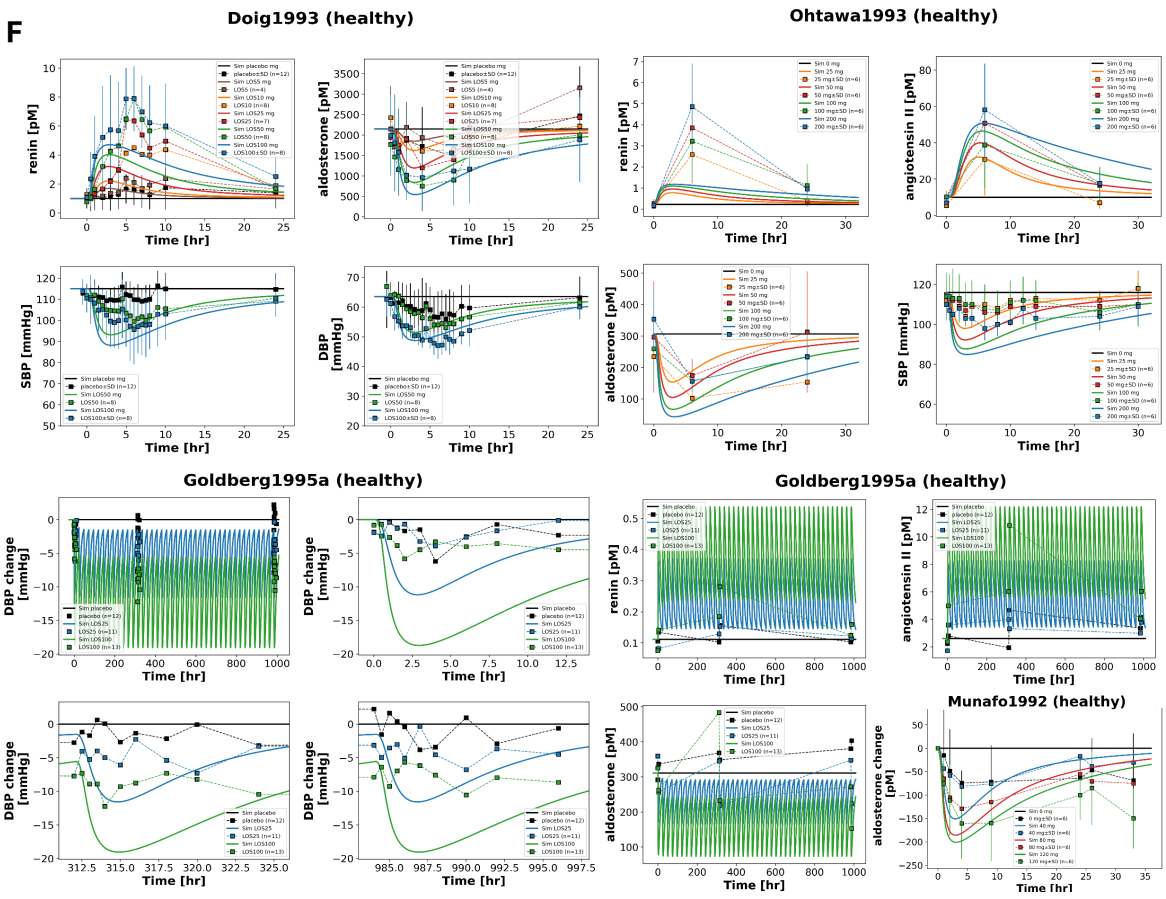


Figure 4. continued: Dose-dependent pharmacokinetics and pharmacodynamics of losartan. (F) Simulated versus observed losartan pharmacodynamics. Data from [16,71,75,76].

3.4. Hepatic Impairment

Figure 5 shows the impact of hepatic dysfunction on the pharmacokinetics and pharmacodynamics of losartan and E3174. As cirrhosis severity increases, losartan plasma and urine concentrations rise, while E3174 levels and the E3174/losartan ratio decrease. Fecal excretion remains largely unchanged, indicating that hepatic impairment predominantly affects metabolic clearance rather than biliary elimination.

Pharmacokinetic analysis reveals increasing AUC, C_{max} , and half-life for both losartan and E3174 with worsening cirrhosis, accompanied by a decline in the elimination rate constant (k_{el}). While losartan accumulation is qualitatively consistent with clinical observations from patients with mild to moderate cirrhosis [8,11], the model underestimates absolute concentrations, particularly for E3174, which shows a delayed but modest increase in plasma levels at higher cirrhosis degrees. This discrepancy likely reflects unaccounted factors such as reduced hepatic blood flow, altered enzyme activity, or additional compensatory mechanisms [27].

Pharmacodynamically, impaired liver function attenuates the formation of E3174 and modifies RAAS regulation. Early renin and angiotensin I responses are reduced, while aldosterone and blood pressure increase initially, with prolonged elevation in more severe cirrhosis. These trends correspond to delayed normalization of hormonal and hemodynamic parameters. Despite sparse PD data and limited control groups, the model reproduces general concentration–time and dose–response patterns, supporting the clinical recommendation of dose adjustment in hepatic impairment. This is particularly relevant for patients with comorbidities such as heart failure, where sensitivity to RAAS inhibition is increased [35,36].

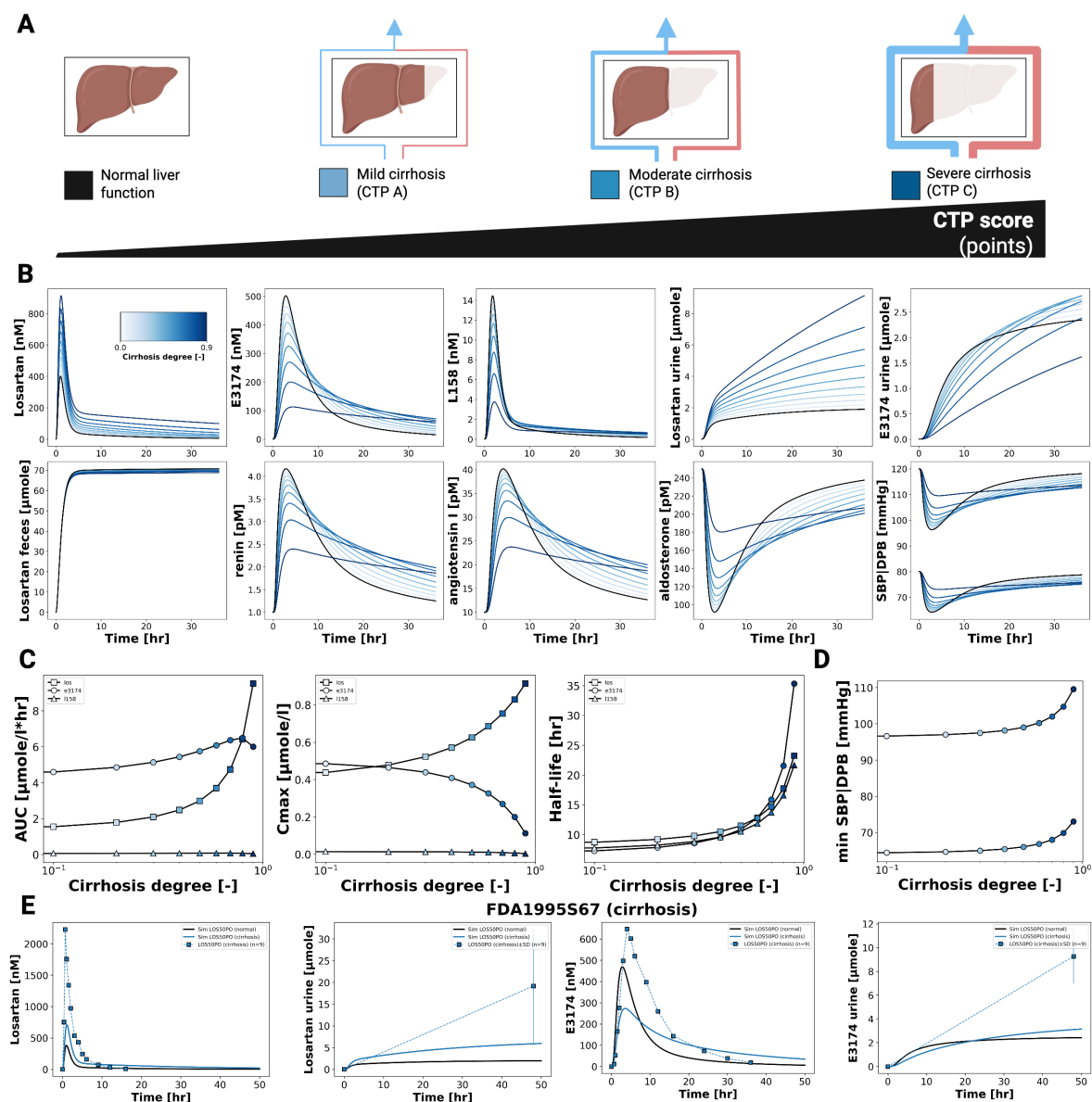


Figure 5. Effect of hepatic impairment on losartan pharmacokinetic and pharmacodynamic profiles. (A) Illustration of the level of cirrhosis evaluated in the simulations. **(B)** Simulated plasma concentrations profiles of losartan, E3174 and L158, urinary excretion profile of losartan and E3174, a fecal excretion profile of losartan, as well as simulated RAAS biomarkers (renin, angiotensin I and aldosterone) and blood pressure responses across cirrhosis degrees. Cirrhosis degree is indicated by line color. **(C)** Cirrhosis degree-dependent curves for AUC, C_{max} and half-life. **(D)** Cirrhosis degree-dependent maximum or minimum values of systolic blood pressure SBP and diastolic blood pressure DBP. **(E)** Simulated (solid lines) versus observed (symbols) pharmacodynamic timecourses for different degrees of cirrhosis in FDA1995S67 [77].

3.5. Renal Impairment

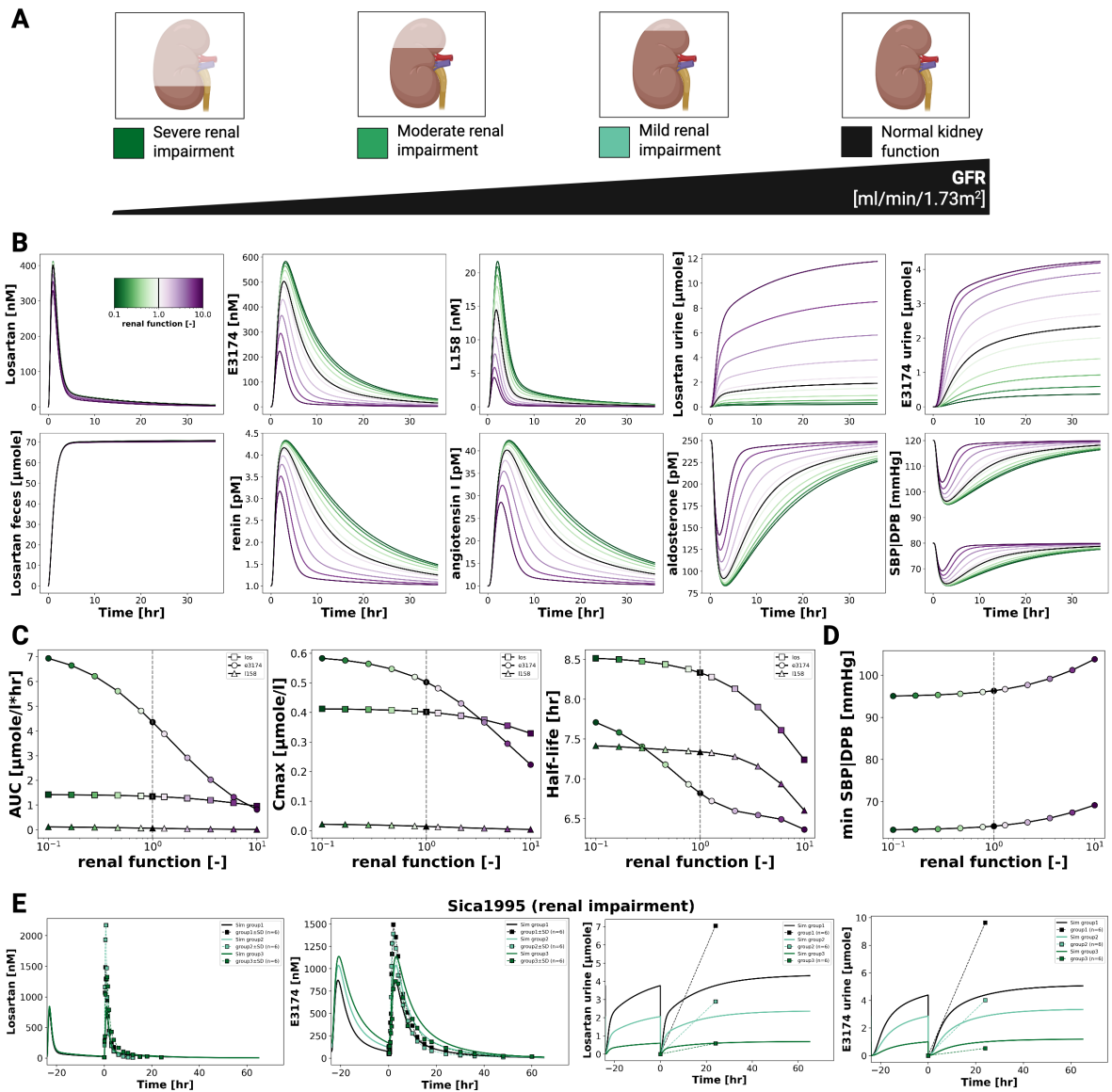


Figure 6. Effect of renal impairment on losartan pharmacokinetics and pharmacodynamic profiles. **(A)** Illustration of the level of renal impairment evaluated in the simulations. **(B)** Simulated plasma concentrations profiles of losartan, E3174 and L158, urinary excretion profile of losartan and E3174, a fecal excretion profile of losartan, as well as simulated RAAS biomarkers (renin, angiotensin I and aldosterone) and blood pressure responses across degrees of renal function. Renal function degree is indicated by line color. **(C)** Renal function-dependent curves for AUC, C_{max} and half-life. **(D)** Renal function-dependent maximum or minimum values of systolic blood pressure SBP and diastolic blood pressure DBP. **(E)** Simulated (solid lines) versus observed (symbols) pharmacokinetic timecourses for different degrees of renal impairment in Sica1995 [19].

Figure 6 illustrates the effect of declining renal function on the pharmacokinetics and pharmacodynamics of losartan and its active metabolite E3174. As renal function decreases, losartan plasma concentrations remain largely unchanged, whereas E3174 levels increase, accompanied by reduced urinary excretion of both compounds. Fecal excretion of losartan shows a slight compensatory rise, and the E3174/losartan ratio increases with impaired renal clearance.

On the pharmacokinetic level, the model predicts stable AUC and C_{max} values for losartan, while E3174 shows rising AUC, C_{max}, and half-life as renal function declines, reflecting reduced clearance. These results align qualitatively with the physiology of renal elimination, though they overestimate

metabolite accumulation compared to clinical findings [19,28], where E3174 exposure remained stable across renal function groups. This discrepancy may indicate unaccounted processes such as altered absorption, metabolism, or hepatic clearance of E3174 [11].

Pharmacodynamically, impaired renal function amplifies losartan's antihypertensive effects. The model predicts stronger suppression of aldosterone and systolic blood pressure, along with compensatory rises in renin and angiotensin I. While direct PD data in renally impaired populations are limited, these predictions are physiologically plausible and extend clinical observations. Nevertheless, the degree of RAAS suppression may be slightly overestimated due to the absence of compensatory mechanisms such as altered hepatic clearance or long-term feedback regulation [36,37,77].

3.6. ABCB1 Genotypes

Figure 7 illustrates the influence of ABCB1 (P-glycoprotein) transporter activity on the pharmacokinetics and pharmacodynamics of losartan and E3174. Simulations across varying transporter activity levels, including common diplotypes (GG/CC, GT/CT, TT/TT), show that reduced ABCB1 activity leads to increased plasma and urinary concentrations of both compounds, while fecal excretion of losartan declines due to decreased intestinal and biliary efflux.

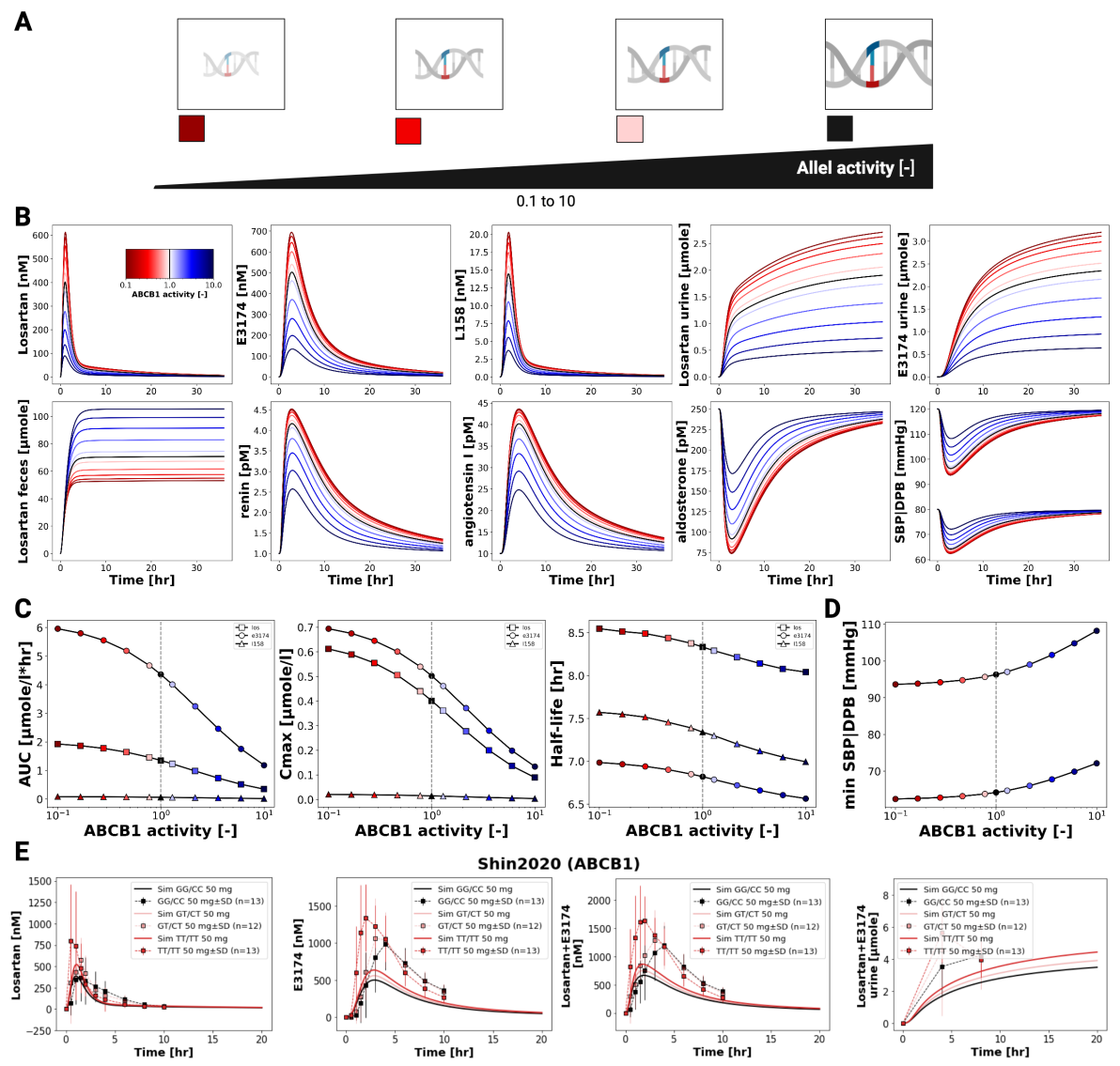


Figure 7. Pharmacokinetics and pharmacodynamics of losartan and metabolites across varying ABCB1 activity levels (A) Illustration of the level of CYP2C9 activity evaluated in the simulations. **(B)** Simulated plasma concentrations and excretion profiles of losartan, E3174 and L158, urinary excretion profile of losartan and E3174, a fecal excretion profile of losartan, as well as simulated RAAS biomarkers (renin, angiotensin I and aldosterone) and blood pressure responses across varying ABCB1 activity. Allel function degree is indicated by color. **(C)** ABCB1 activity-dependent curves for AUC, C_{max} , elimination rate constant k_{el} , and half-life. **(D)** ABCB1 allele activity-dependent maximum or minimum values of systolic blood pressure SBP and diastolic blood pressure DBP. **(E)** Simulated (solid lines) versus observed (symbols) pharmacodynamic timecourses for different degrees of ABCB1 activity in Shin2020 [32].

Pharmacokinetic analysis indicates modest increases in AUC and C_{max} for losartan and E3174 with lower ABCB1 activity, whereas elimination rate constants (k_{el}) and half-life remain largely unchanged. The plasma and urine E3174/losartan ratio decreases slightly under low transporter activity. These trends are qualitatively consistent with clinical observations [32], although absolute concentrations are slightly underestimated by the model.

Pharmacodynamically, reduced ABCB1 activity slightly enhances RAAS-related effects, including modest increases in renin and angiotensin I and marginal reductions in aldosterone and blood pressure. While these changes are small and unlikely to necessitate dose adjustments based on ABCB1 diplotype alone, the model demonstrates the capacity to predict subtle genotype-dependent differences in drug exposure and pharmacodynamic response. Future refinement could include better representation of

renal P-gp expression and its contribution to systemic clearance, as well as additional clinical data on pharmacodynamic outcomes to improve predictive accuracy [32].

3.7. CYP2C9 Genotypes

Figure 8 illustrates the impact of CYP2C9 genetic variability on the pharmacokinetics and pharmacodynamics of losartan and its active metabolite E3174. Simulations across a continuous range of CYP2C9 activity, as well as genotype-specific simulations for *1/*1, *1/*2, *1/*3, *1/*13, *2/*2, *2/*3, and *3/*3, demonstrate that reduced enzyme activity leads to impaired metabolic conversion, resulting in higher plasma, urine, and fecal levels of losartan and decreased E3174 exposure.

Pharmacodynamically, lower CYP2C9 activity diminishes RAAS inhibition, with smaller reductions in aldosterone and systolic blood pressure, and attenuated compensatory increases in renin and angiotensin I. AUC and $C_{\max}$ for losartan rise with declining enzyme activity, while E3174 exposure decreases; elimination rate constants and half-life remain relatively stable. These model predictions are consistent with clinical observations, which report 1.6- to 3-fold increases in losartan AUC and significantly reduced E3174 levels in carriers of reduced-function alleles [35–37], although absolute concentrations tend to be slightly underestimated.

The use of a continuous CYP2C9 activity scale enables the simulation of nonlinear relationships between enzyme activity and metabolite formation across a spectrum of genotypes. While CYP2C9 genotype is a major determinant of inter-individual variability, other factors such as age, comorbidities, and concomitant medications may further influence pharmacokinetics and pharmacodynamics. From a clinical perspective, these findings support the potential of genotype-guided dosing for patients with reduced-function alleles, although high variability within genotype groups suggests that genetic testing should be applied selectively, focusing on individuals with inadequate response or elevated risk of adverse effects.

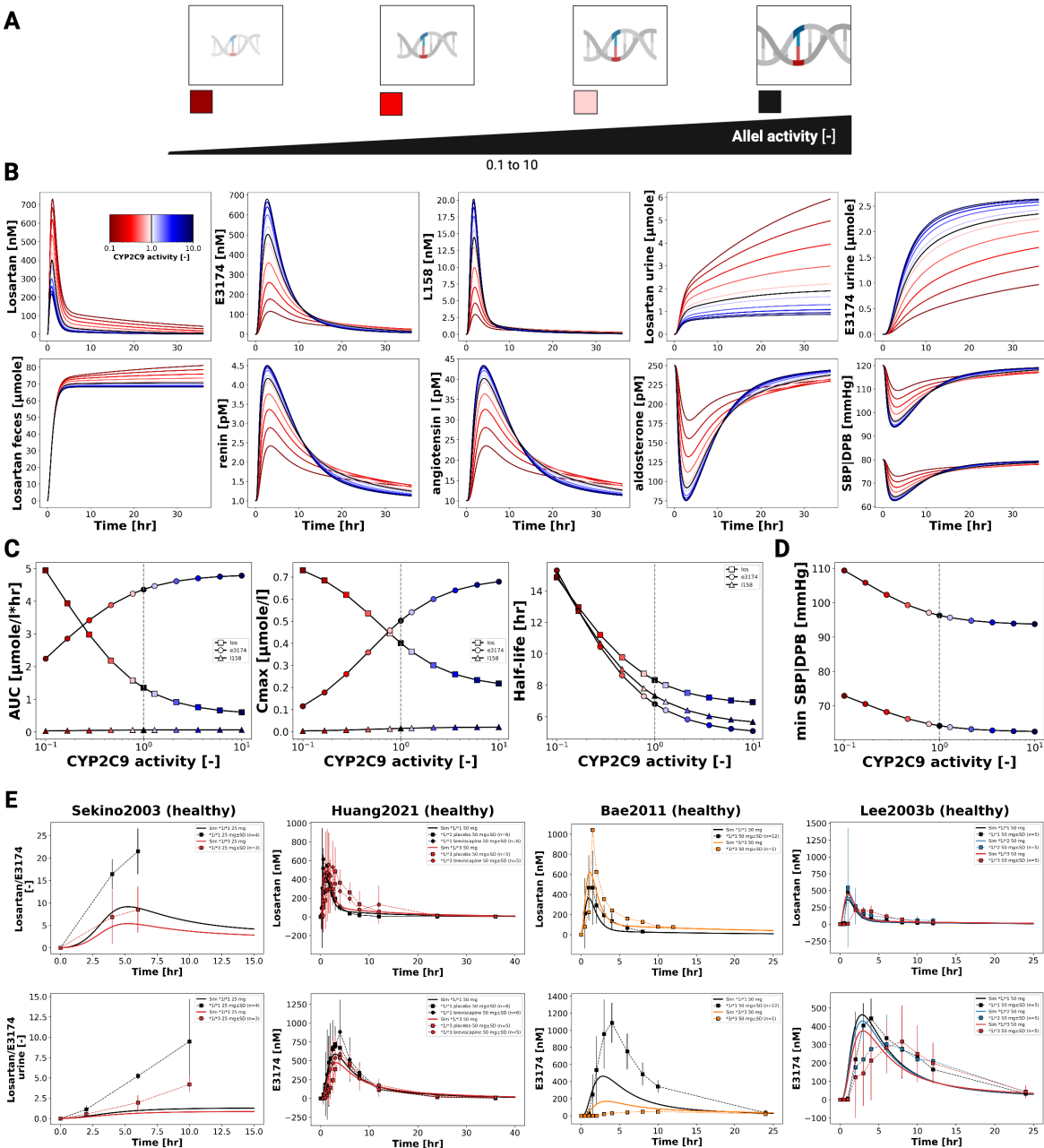


Figure 8. Pharmacokinetics and pharmacodynamics of losartan and metabolites across varying CYP2C9 activity levels. (A) Illustration of the level of CYP2C9 activity evaluated in the simulations. (B) Simulated plasma concentrations and excretion profiles of losartan, E3174, L158 and E3174/losartan ratio under varying CYP2C9 activity. (C) CYP2C9 activity-dependent curves for AUC, C_{max} , elimination rate constant k_{el} , and half-life. (D) CYP2C9 allele activity-dependent maximum or minimum values of systolic blood pressure SBP and diastolic blood pressure DBP. (E) Simulated versus observed losartan pharmacokinetics. Data from [36,64,67,70].

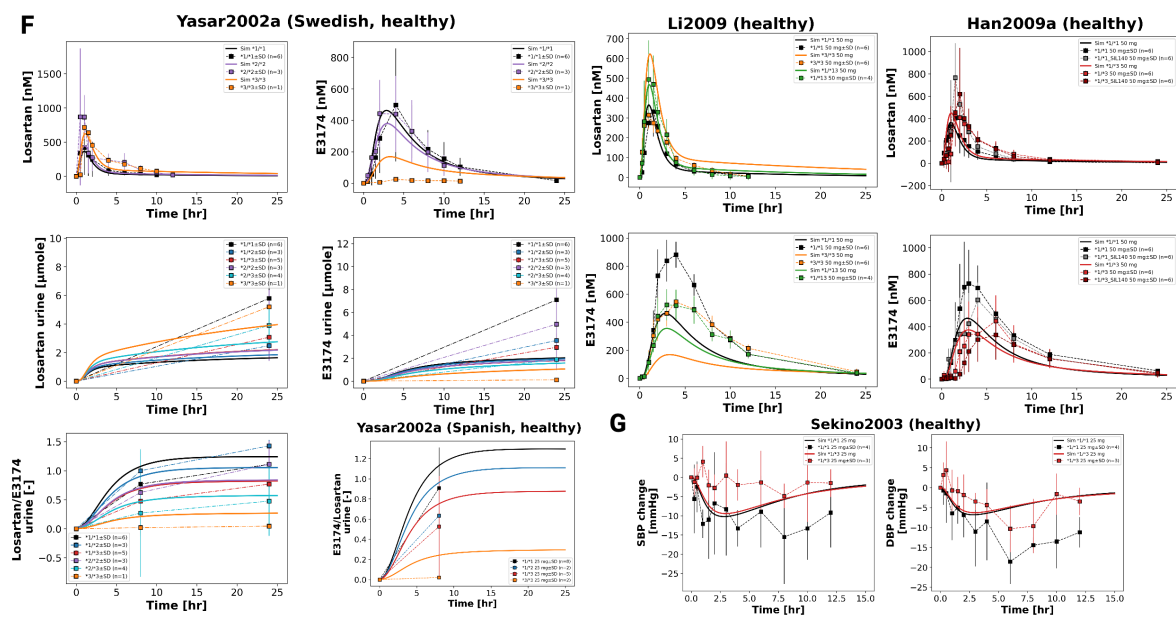


Figure 9. continued: Pharmacokinetics and pharmacodynamics of losartan and metabolites across varying CYP2C9 activity levels. (F) Simulated versus observed losartan pharmacokinetics. Data from [35,40,66]. Simulated versus observed SBP and DBP for different CYP2C9 genotypes [36].

4. Discussion

In this study, we developed and evaluated a physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) model of losartan, informed by a curated database of 24 clinical studies covering diverse dosing regimens, populations, and physiological conditions. The model integrates intestinal absorption, hepatic metabolism via CYP2C9, and renal excretion, while linking systemic exposure of the active metabolite E3174 to downstream pharmacodynamic effects through a simplified RAAS submodel. This framework enables simulation of losartan and metabolite concentrations in plasma, urine, and feces, as well as prediction of pharmacodynamic endpoints such as renin, angiotensin I, aldosterone, and systolic blood pressure under baseline and perturbed conditions. By reproducing key clinical observations, the model demonstrates its potential to provide mechanistic insights into inter-individual variability and support personalized dosing strategies.

The curated database was essential for calibration and validation of the model, but it also highlights important limitations. While losartan pharmacokinetics are well characterized, data on RAAS dynamics remain limited, particularly with respect to circadian variability and long-term feedback regulation. Excretion data—especially for fecal elimination and the secondary metabolite L158—were sparse, and pharmacodynamic datasets showed high variability across studies. These gaps restrict the predictive accuracy of the model under complex physiological conditions but do not preclude its use in capturing system-level dose–exposure–response relationships.

Our dose dependency simulations reproduced the nonlinear pharmacokinetics of losartan and E3174, demonstrating a decreasing metabolite-to-parent ratio at higher doses due to saturable CYP2C9 metabolism. Consistent with clinical findings, increasing doses resulted in stronger and more sustained suppression of aldosterone and systolic blood pressure, accompanied by compensatory increases in renin and angiotensin I. This supports the model’s ability to capture both nonlinear PK behavior and dose-dependent RAAS responses.

In hepatic impairment, the model predicted elevated losartan plasma concentrations, reduced clearance, and attenuated metabolite formation, reflecting impaired CYP2C9 metabolism and hepatic blood flow. While the model underestimated the reported accumulation of E3174 in cirrhosis, it nonetheless confirmed the need for dose reduction in patients with liver dysfunction, particularly in comorbid conditions such as heart failure where sensitivity to RAAS inhibition is heightened.

Renal impairment simulations predicted reduced clearance of both losartan and E3174, leading to prolonged systemic exposure. While these results are qualitatively consistent with PK data, the model overestimated E3174 accumulation compared to reported clinical findings. Importantly, in the absence of PD data from impaired populations, the model allowed prediction of enhanced RAAS suppression and blood pressure reduction—although these effects may be slightly exaggerated due to the omission of compensatory mechanisms.

Genetic variability was also explored. For CYP2C9, the model captured the pronounced impact of reduced-function alleles on E3174 formation and downstream pharmacodynamic effects, reproducing the diminished blood pressure reduction observed clinically. The use of a continuous enzyme activity scale enabled simulation across a spectrum of genotypic variability. In contrast, ABCB1 (P-gp) variability had only minor effects on systemic exposure and blood pressure, consistent with limited clinical data, although the model suggests possible contributions via altered intestinal efflux and renal secretion. These findings emphasize the potential of PBPK/PD modeling to disentangle the contributions of genetic variability to losartan response.

Looking forward, several opportunities for refinement exist. Incorporating circadian rhythm, sodium and water balance, and autonomic feedback would enhance physiological fidelity of the RAAS submodel. Expanding datasets for fecal excretion, L158 kinetics, and pharmacodynamic outcomes would strengthen calibration. Future model extensions could also integrate additional sources of variability, such as age, comorbidities, or transporter–enzyme interactions, to support population-level simulations. Ultimately, the losartan PBPK/PD framework provides a mechanistically grounded platform for exploring inter-individual variability and optimizing dosing strategies, with potential applications in precision medicine and clinical decision support.

5. Conclusions

In this study, a comprehensive physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) model of losartan was developed and validated using an extensive clinical database. The model successfully reproduced key pharmacokinetic and pharmacodynamic behaviors, including dose-dependent RAAS inhibition and nonlinear metabolite formation resulting from saturable CYP2C9 metabolism. Simulations captured the attenuated pharmacodynamic response under hepatic impairment and predicted enhanced RAAS suppression in renal dysfunction. Furthermore, the model quantified the pronounced impact of CYP2C9 genetic variability on metabolite exposure and blood pressure effects, while ABCB1 activity contributed only minor modulation of systemic exposure.

Despite certain limitations in clinical data and model scope, the framework provides valuable mechanistic insight into inter-individual variability in losartan response. It highlights the potential of systems pharmacology modeling to support dose optimization across physiological and genetic conditions. Together, the losartan database and PBPK/PD model establish a solid foundation for future integration into digital twin platforms and personalized therapy design.

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Data Availability Statement: All curated pharmacokinetic data are publicly available in the PK-DB database (<https://pk-db.com>). The model and all associated materials (simulation scripts, parameters, and documentation) are publicly available in SBML format under a CC-BY 4.0 license at <https://github.com/matthiaskoenig/losartan-model> [52].

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