

Renal function shapes the timing of free-digoxin rebound after digoxin-specific antibody fragments: a coupled-kinetics model

Tian-Yu Wang

wangty0709@hotmail.com

Guangdong Peizheng College

Research Article

Keywords: Digoxin, Digoxin-specific antibody fragments, Rebound, Renal function, Coupled kinetics, Pharmacokinetic modelling

Posted Date: October 8th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11175177/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Renal function shapes the timing of free-digoxin rebound after digoxin-specific antibody fragments: a coupled-kinetics model

Article type Original research paper

Author Tian-Yu Wang

Affiliation Medical Office, General Affairs Office, Guangdong Peizheng College, Guangzhou 510830, Guangdong, China

Corresponding author Tian-Yu Wang, Medical Office, General Affairs Office, Guangdong Peizheng College, Guangzhou 510830, Guangdong, China. E-mail: wangyu0709@hotmail.com. ORCID: 0000-0002-5124-7965

Abstract

Purpose Free digoxin falls after digoxin-specific antibody fragments (Fab), then rebounds. A fixed additional clearance carries no antibody or complex mass, so it cannot give the duration of suppression. We asked when the rebound peaks, how high it rises, and how renal function changes both.

Methods Digoxin occupied central, fast-tissue and deep-tissue compartments and Fab one, with an explicit Fab–digoxin complex at mass-action equilibrium. Exchange and elimination tracked non-Fab-bound plasma digoxin and creatinine clearance. Four renal strata and an acute-kidney-injury scenario were simulated at the labelled dose against a fixed-clearance comparator.

Results In the reference scenario (labelled dose, single ingestion), free digoxin peaked 90.0 h after Fab with normal renal function and 291.5 h with dialysis-dependent kidney failure (ratio 3.24), and 187.0 h when renal function fell acutely; the fixed-clearance comparator gave 66.0 h at all strata (ratio 1.00). In the dose-aligned scenario matched to the published cohort, the rebound peak was 0.361 nmol/L at $1 \times 10^{10} \text{ M}^{-1}$, 4.70-fold below the observed mean of $1.7 \pm 1.3 \text{ nmol/L}$, and 1.083 nmol/L at $1 \times 10^9 \text{ M}^{-1}$. Free digoxin stayed below 2.6 nmol/L in all strata except at sub-neutralising doses. Terminal half-life (1.83, 3.55 d) and convergence (6.9×10^{-7}) met criteria.

Conclusion Renal function, not dose alone, set when free digoxin rebounded; a fixed-clearance construct is flat by construction. Rebound amplitude depended strongly on antibody affinity; the labelled upper bound was incompatible with observed peaks. These predictions did not meet pre-specified criteria; no dosing recommendation follows.

Keywords Digoxin; Digoxin-specific antibody fragments; Rebound; Renal function; Coupled kinetics; Pharmacokinetic modelling

Introduction

Digoxin-specific antibody Fab fragments are the definitive treatment for life-threatening digoxin toxicity. They entered practice in 1976, after the first patients treated recovered from advanced intoxication [1], and they are now first-line monotherapy for severe poisoning [2, 3]. The dose is not titrated against a measured response; it is computed from an estimate of the total body burden (a reported ingested amount, or a serum concentration multiplied by body weight) and given as a single course [4]. That construction has long been questioned. The lowest effective regimen has never been established, and the equations in current use make no allowance for lean body weight, age, or renal failure [5]. Recent expert consensus still lists dosing and monitoring among its open questions [6, 7], and practice has moved ahead of the evidence, with smaller titrated doses for acute poisoning in at least one national service [8, 9].

A burden-based dose is static. The antibody binds digoxin in the circulation and removes the free drug, but the bulk of the body burden sits in tissue and keeps exchanging with plasma. As free antibody declines, digoxin the antibody had drawn out of tissue returns to the circulation in free, active form [10]. Free digoxin therefore does not stay suppressed; it falls to a nadir and then rises. Ujhelyi and colleagues documented the pattern in 14 patients: free digoxin fell rapidly and then rebounded to a mean maximum of 1.7 ± 1.3 nmol/L after 77 ± 46 h, and the rise came later in the end-stage renal disease subgroup (127 ± 40 h) than in the others (55 ± 28 h) [11]. Late, sometimes severe rebound in anuric patients has been reported since [12]. How long one dose keeps free digoxin suppressed, and when the rise begins, is not part of the dose calculation.

Pharmacokinetic models have not supplied it. Adult digoxin pharmacokinetics are well described by population models, usually one compartment [13], and physiologically based models exist for heart failure [14, 15]. The antibody has its own kinetics, including in renal failure [16, 17, 18, 19], and its affinity has been measured by equilibrium dialysis [20, 21, 22]. They have rarely been coupled. The one study to examine Fab dosing directly is the digoxin PBPK model of Bracken and colleagues [23]. Two of its findings frame this work. First, it identified the key to efficient and cost-effective dosing as avoiding the "mismatch between timing of digoxin Fab and the redistribution of digoxin back into the circulation". Second, doses far below those needed for full or half neutralisation were sufficient, while a large bolus did not prevent substantial rebound in one patient. In that model, however, the antibody has no time course of its own: the effect is an additional total clearance of digoxin inside the plasma compartment, with binding assumed to occur at a fixed 1:1 ratio. Its authors note that clearing digoxin from plasma is not physiologically consistent and that the 1:1 assumption has limited substantiation. Neither Fab nor complex is tracked, so the added clearance has no capacity and never decays with the antibody; the model cannot say how long a dose holds. Bracken and colleagues left the timing of doses to future work.

We therefore built a model in which the antibody and its complex with digoxin are represented explicitly (the antibody has its own disposition and the complex its own clearance), with binding treated as an instantaneous mass-action equilibrium rather than an additional differential state, and set this against a fixed-additional-clearance comparator

calibrated once at normal renal function and held constant thereafter. Tissue exchange here is driven by the free, non-Fab-bound plasma concentration, which is what allows a rebound to arise at all. We asked three questions. When does free digoxin rebound after a single label dose, and how high does it go? Does the answer depend on renal function, including acute kidney injury? And for how long does the current single dose keep free digoxin below the concentration that triggered treatment? Because the relation between free digoxin concentration and clinical toxicity is unknown, we use mechanistic endpoints: the time to the post-nadir maximum, as defined in the clinical literature [11], with the treatment-trigger threshold retained only as a conditional secondary endpoint.

Methods

Model structure

We built a coupled digoxin–Fab kinetic model in which the antibody and its complex are explicit state variables rather than a modification of digoxin clearance. The state vector holds five amounts: gut digoxin, total digoxin and total Fab in a central compartment, and digoxin in fast and deep peripheral compartments, the deep one representing the Na^+/K^+ -ATPase pool. The labelled apparent volume of distribution, 475–500 L [24], rules out a single compartment [13, 25].

Binding was instantaneous mass action, $C/V_c = K_a \cdot 10^{-9} \cdot (D_{\text{tot}} - C) \cdot (F_{\text{tot}} - C)/V_c^2$, solved in closed form at every right-hand-side evaluation, taking the smaller root. The complex therefore carries no dissociation rate constant: at 10^{10} M^{-1} its relaxation time is far shorter than any transport or clearance timescale here.

One structural choice governs whether such a model can rebound: both tissue fluxes are driven by the free, non-Fab-bound central concentration, never by the total amount. Fab lowers it, the deep compartment is left above its equilibrium with plasma, and the deep flux reverses; because the clearances act on that concentration, loss of the tissue gradient and protection from elimination follow from one term.

Parameters

Digoxin parameters came from the label and published analyses: absorption rate constant 1.22 h^{-1} [26]; unbound plasma fraction 0.71 [14]; apparent volume of distribution 475–500 L; terminal half-life 1.5–2.0 d normally and 3.5–5.0 d in anuria; 50–70% recovered unchanged in urine [24, 27]. Total clearance at normal renal function was derived, 130 mL/min from $\ln 2 \cdot V_d/t_{1/2}$ at $t_{1/2} = 42.2 \text{ h}$, and split equally between renal and non-renal routes. Renal clearance was proportional to creatinine clearance (CrCl) [24, 28], with filtration set equal to it.

Fab received the labelled volume of distribution 0.3 L/kg [4, 29] and a systemic clearance of 0.32 mL/min/kg at normal renal function [16], falling to the reported ESRD value of 0.057 mL/min/kg [18]; the interpolation between them (a factor $0.18 + 0.82 \cdot \text{CrCl}/100$) is ours. The complex is cleared renally at $\text{CL}_C = \theta \cdot \text{CrCl}$ with $\theta = 0.1$, since a $\sim 47 \text{ kDa}$ complex sits just

below the filtration threshold [3, 22]; no measurement against GFR was found, so θ is provisional and scanned over 0–1.

Other required quantities are declared as assumptions: central volume 0.3 L/kg (equal to the Fab volume of distribution); apparent volume split 130 L fast and 324 L deep; fast-tissue exchange 2.0 h^{-1} ; deep-tissue exchange 0.4 h^{-1} , calibrated so that the measured end of the distribution phase is 6.8 h, inside the labelled 6–8 h [24]; 869.6 nmol of binding sites per 40 mg vial [4], against 641.0 nmol if the label's 0.5 mg binding capacity is read as the site count, a 1.36-fold excess carried as a declared sensitivity; and oral bioavailability $F = 0.8$ applied on both sides of the dose calculation. Protein binding, about 25% [24], was not modelled.

Scenarios and comparator model

Four stable strata were simulated, at CrCl 100, 60, 30 and 15 mL/min (KDIGO G1–G2, G3a–G3b, G4 and G5 [30]); CrCl was estimated by Cockcroft–Gault [31] and held constant, and dialysis was not modelled [24]. A separate acute kidney injury scenario had CrCl fall linearly from 90 to 30 mL/min over 48 h and hold at 30 thereafter, so renal function inside the equations is genuinely time-varying [32]. The reference case was a 70 kg adult ingesting 10 mg digoxin, with Fab at 6 h and a 21 d horizon; the dose was a multiple of the label Formula-1 dose, vials = body load in mg $\div$ 0.5 [4], at multipliers 0.5, 1, 2 and 4, with a finer 0.25, 0.5 and 0.75 grid used only to locate where suppression fails.

The published alternative implements the antibody as a fixed additional digoxin clearance that switches on with the Fab bolus and never decays, with no Fab and no complex as state variables [23]; we reproduced that structure. Its constant was calibrated once, in the normal-renal-function label-dose scenario, so that its post-Fab nadir matched the coupled model's, and held constant everywhere. The comparison is not a test of whether that model rebounds, since a constant extra clearance can only remove drug; the testable quantity is the renal gradient in rebound time.

Endpoints

The primary endpoint was t_{peak} , the time from Fab to the maximum free digoxin concentration after the post-Fab nadir. This is the operational definition used in the anchor study [11], and it is defined in every scenario, because free digoxin passes a minimum after any finite antibody dose. Threshold crossing, the first upward crossing of 2.6 nmol/L after the nadir and the criterion adopted in ATOM-6 [9], was unusable as a primary endpoint: it asks whether free digoxin returns to the concentration that triggered treatment, which after neutralisation it does not. It was therefore kept as a conditional secondary endpoint, reported only at sub-neutralising doses. Secondary endpoints were the nadir, the rebound peak and the time to nadir; the terminal half-life and distribution-phase end served as self-consistency checks [24].

Numerical implementation and checks

Integration used LSODA [33] through `scipy.integrate.solve_ivp` [34] at relative and absolute tolerances of 10^{-8} and 10^{-10} (amounts in nmol). The Fab bolus is a discontinuity, so integration was split at each dosing time and restarted from the post-bolus state. Endpoints came from a uniform output grid (0.5 h for the strata and verification runs, 0.25 h for the

dose-aligned anchors, 1 h for the two scans). Convergence was checked by re-integrating the reference scenario at five progressively tighter tolerances, the criterion being a relative change in the rebound peak below 10^{-3} . Sensitivity was assessed one parameter at a time at 0.5 and 2 times the reference value as the log–log elasticity of t_{peak} [35].

Criteria were fixed in advance in three blocks. V3 compared the terminal half-life at normal and anuric renal function with the labelled ranges and the distribution phase with the labelled 6–8 h. V2 asked whether rebound persists at four times the label dose, whether a sub-neutralising dose still suppresses free digoxin, and whether the published single-patient case still rebounds. V1 set five criteria against the only two anchors available: t_{peak} inside 55 ± 28 h and the peak inside 1.7 ± 1.3 nmol/L in the non-ESRD scenario, ESRD slower than non-ESRD, the single-patient case still rebounding, and the dose alignment landing in the anchor's pre-Fab range. Because the anchor doses by measured concentration, the model was aligned on the pre-Fab total digoxin concentration, and its non-ESRD subgroup's unreported renal function was proxied by CrCl 30.

During the preparation of this work, the author used Kimi K3 (Moonshot AI) to assist with model implementation, numerical analysis, and the drafting of the manuscript. The author reviewed and edited all content and takes full responsibility for the integrity and accuracy of the published article.

Results

The rebound peak comes later as renal function falls

Free digoxin reached its nadir within 0.5 h of the bolus in every stratum; its post-nadir maximum came later as renal function fell: 90.0, 133.0, 207.0 and 291.5 h after Fab at $K_a = 1 \times 10^{10} \text{ M}^{-1}$, and 61.5, 90.5, 141.0 and 198.0 h at $K_a = 1 \times 10^9 \text{ M}^{-1}$ (Fig 1, Table 1). In the acute kidney injury scenario the peak fell between the CrCl 60 and 30 strata, at 187.0 and 120.0 h.

Table 1 Primary endpoint after a single label dose, by renal stratum and binding affinity

Stratum	CrCl (mL/min)	t_{peak} , $K_a 10^{10} \text{ M}^{-1}$ (h)	t_{peak} , $K_a 10^9 \text{ M}^{-1}$ (h)	Peak, $K_a 10^{10} \text{ M}^{-1}$ (nmol/L)	Peak, $K_a 10^9 \text{ M}^{-1}$ (nmol/L)	Crossing of 2.6 nmol/L
Normal	100	90.0	61.5	0.455	1.717	not crossed
Moderate CKD	60	133.0	90.5	0.515	1.838	not crossed
Severe CKD	30	207.0	141.0	0.638	2.080	not crossed
ESRD	15	291.5	198.0	0.805	2.391	not crossed
Acute kidney	90 → 30 over 48 h	187.0	120.0	0.584	1.899	not crossed

injury						
--------	--	--	--	--	--	--

t_{peak} is hours from Fab to the post-nadir free digoxin maximum; Peak is that maximum. The label dose is 16 vials, 640 mg, at 70 kg. The 2.6 nmol/L criterion is the ATOM-6 treatment threshold [9] and is not crossed within 21 d anywhere.

The label dose holds the free concentration down

The 2.6 nmol/L criterion was never re-crossed after the nadir at the label dose, in any stratum or at either affinity (Table 1). Fig 2 scans the two parameters the literature does not identify, θ and k_{deep}: at the upper affinity it is re-crossed nowhere on the grid within 21 d, including at $\theta = 0$; at the lower affinity only for $\theta \leq 0.05$. Crossing occurred only at sub-neutralising doses: at 0.25 and 0.5 times the label dose for $K_a = 1 \times 10^9 \text{ M}^{-1}$ (19.9 h at normal renal function, 48.1 h at ESRD at the 0.5 multiple; Fig 3) and only at 0.25 times for $K_a = 1 \times 10^{10} \text{ M}^{-1}$ (2.4 and 2.3 h).

Only the coupled model produces a renal gradient

The published structure is implemented here as a single calibrated extra clearance, 55.1 and 33.5 L/h at the two affinities, 7.1 and 4.3 times digoxin's total clearance, with no renal dependence (Fig 4). Its t_{peak} was 66.0 h in every stratum (Table 2). The coupled model ranged from 61.5 to 198.0 h at $K_a = 1 \times 10^9 \text{ M}^{-1}$ (ratio 3.22) and from 90.0 to 291.5 h at the upper affinity (ratio 3.24). The two comparisons differ in kind: the stable strata have no cohort counterpart, so the flat-versus-steep contrast is structural rather than a test against data, while the comparison against the anchor uses its dose-aligned scenario, where the model's ESRD-to-non-ESRD ratio was 1.41 at $K_a = 1 \times 10^{10} \text{ M}^{-1}$ and 1.39 at $K_a = 1 \times 10^9 \text{ M}^{-1}$ against the observed 2.31, an under-prediction of about 1.6-fold.

Table 2 Renal gradient in rebound time: structural discrimination on stable strata, and the dose-aligned comparison with the anchor

Comparison basis	Model or source	t _{peak} , four strata or two subgroups (h)	Spread (h)	ESRD / comparator
Stable strata, CrCl 100 → 15; no cohort counterpart exists, so this contrast is structural and not a test against data	Fixed clearance, $K_a 1 \times 10^{10} \text{ M}^{-1}$	66.0 / 66.0 / 66.0 / 66.0	0.0	1.00
	Coupled model, $K_a 1 \times 10^{10} \text{ M}^{-1}$	90.0 / 133.0 / 207.0 / 291.5	201.5	3.24
	Fixed clearance, $K_a 1 \times 10^9 \text{ M}^{-1}$	66.0 / 66.0 / 66.0 / 66.0	0.0	1.00
	Coupled model, $K_a 1 \times 10^9 \text{ M}^{-1}$	61.5 / 90.5 / 136.5 / 198.0	136.5	3.22

	$K_a \ 1 \times 10^9 \text{ M}^{-1}$	141.0 / 198.0		
Dose-aligned anchor scenario, CrCl 30 → 15, non-ESRD → ESRD	Coupled model, $K_a \ 1 \times 10^{10} \text{ M}^{-1}$	173.75 / 244.75	—	1.41
	Coupled model, $K_a \ 1 \times 10^9 \text{ M}^{-1}$	102.75 / 143.25	—	1.39
	Observed [11]	$55 \pm 28 \text{ (n = 10)}$ $/ 127 \pm 40 \text{ (n = 4)}$	—	2.31

The first block uses the stable strata of Table 1 (CrCl 100 to CrCl 15), its ratio being ESRD over normal; the second uses the doses the anchor gave, aligned on the pre-Fab total concentration, with its non-ESRD subgroup proxied by CrCl 30 and its ESRD subgroup by CrCl 15, its ratio being ESRD over non-ESRD. Observed values are subgroup means ± 1 SD from Ujhelyi 1993 [11], which did not report its non-ESRD subgroup's renal function.

The labelled upper affinity cannot reproduce the observed rebound

Because the anchor doses by measured concentration, the comparison used the doses it gave, aligned on the pre-Fab total concentration. The alignment is checkable: 3.0 mg ingested at $F = 0.8$ puts the simulated pre-Fab total at 5.97 nmol/L at CrCl 30 and 6.03 at CrCl 15, inside the observed 3.5 to 10.5 nmol/L, and the label formula returns 4.8 vials. Against the observed rebound peak of 1.7 ± 1.3 nmol/L, the model peak was 0.361 nmol/L at $K_a = 1 \times 10^{10} \text{ M}^{-1}$, 4.70 times below the mean and outside the ± 1 SD band, 1.083 nmol/L at $K_a = 1 \times 10^9 \text{ M}^{-1}$, inside that band but below the mean, and 0.052 nmol/L at the Digibind affinity of $3.4 \times 10^{11} \text{ M}^{-1}$ [20], 32.5 times below the mean. Within the labelled affinity range [4, 22] the model is reconciled with the observed amplitude only at its lower end.

Quantitative agreement with the anchor was not obtained

Against the two published anchors the model failed, and the failure is reported as measured. Of the five criteria fixed in advance, three were reproduced (the direction of the renal effect, the single-patient rebound and the dose alignment), and the two quantitative criteria were not met at either affinity. In the dose-aligned anchor scenario, t_{peak} was 173.75 h at $K_a = 1 \times 10^{10} \text{ M}^{-1}$, 102.75 h at $K_a = 1 \times 10^9 \text{ M}^{-1}$ and 265.5 h at the Digibind affinity, against an observed non-ESRD value of 55 ± 28 h, so the first criterion failed at all three affinities. The second failed at the upper affinity and at the Digibind affinity, falling 4.70 and 32.5 times below the observed mean, and passed only at $K_a = 1 \times 10^9 \text{ M}^{-1}$. The failure is two-sided: the peak is under-predicted at high affinity, the rebound time over-predicted at the anchor's degree of renal impairment.

The verdict is proxy-sensitive, which is part of the finding: the anchor does not report its non-ESRD subgroup's renal function, so the criterion was declared on CrCl 30, the model's severe CKD stratum. Had the proxy been CrCl 60 or normal renal function, the criterion would have passed at $K_a = 1 \times 10^9 \text{ M}^{-1}$ (66.5 and 45.25 h); at the upper affinity only the normal-renal

stratum, 75.5 h, falls inside the window. At $K_a = 1 \times 10^9 \text{ M}^{-1}$ the ESRD proxy itself, 143.25 h, falls inside the observed $127 \pm 40 \text{ h}$ window; at the upper affinity it does not, at 244.75 h. The declared proxy was kept and the verdict left as a failure.

Sensitivity and re-dosing

One-at-a-time sensitivity of t_{peak} (Online Resource 1) ranks the central volume first at both affinities (elasticity 0.85 and 0.78), θ fourth at the upper affinity (−0.28), third at the lower (−0.51). The deep- and fast-tissue parameters lie below 0.05, so deep-tissue uncertainty does not drive the rebound time.

A second identical label dose 72 h after the first, under a rule fixed in advance, lowered the ESRD rebound peak from 0.805 to 0.606 nmol/L at the upper affinity and from 2.391 to 1.693 nmol/L at the lower, and moved t_{peak} from 291.5 to 402.0 h and from 198.0 to 304.0 h, while at normal renal function and the upper affinity the peak barely moved, from 0.455 to 0.421 nmol/L (Online Resource 2). These describe behaviour under a pre-specified rule, not a dosing strategy.

Self-consistency and qualitative checks passed

V3 passed: terminal half-life 1.83 d at CrCl 100 and 3.55 d at CrCl 1, the label's anuric reference (labelled 1.5–2.0 and 3.5–5.0 d), and the distribution phase ended at 6.8 h (labelled 6–8 h [24]). Convergence passed too: the largest relative change in the rebound peak across the tolerance ladder was 6.9×10^{-7} against the pre-declared 10^{-3} , with t_{peak} 90.0 h at every setting (Online Resource 3). One check is flagged rather than passed: the Fab clearance used here implies a half-life of 10.83 h, not the labelled 15 h; forcing 15 h raises the reference t_{peak} by 24.4% and about halves the rebound peak. V2 passed all three of its questions: rebound persisted at four times the label dose (peak 0.254 nmol/L, normal renal function), a half label dose still suppressed free digoxin (nadir 0.0296 nmol/L), and the published single-patient case, 25 mg ingested with a single 800 mg bolus at 14 h [23], still rebounded at every affinity, with peaks of 1.196, 4.172 and 0.157 nmol/L at CrCl 30.

Discussion

Principal findings. First, rebound is renal-dependent. In the coupled model the time from dosing to the post-nadir maximum of free digoxin rose from 90 h at normal renal function to 291.5 h at ESRD, a range of 201.5 h and an ESRD-to-normal ratio of 3.24 across the stable strata. That ratio is the structural comparison and it has no cohort counterpart: the fixed-additional-clearance model was flat at 66 h in every stratum, a ratio of 1.00, and across the clearances we scanned (including the one calibrated to reproduce its own initial suppression), it produced no post-nadir rise. The decisive difference is that its antibody term is a constant, with no time course and no renal dependence, so it cannot predict a renal gradient however it is calibrated. In the dose-aligned scenario that mirrors the cohort, the model's ESRD-to-non-ESRD ratio is 1.41 against the observed 2.31, whose constituent means are $127 \pm 40 \text{ h}$ and $55 \pm 28 \text{ h}$ [11]: the direction is reproduced, but that contrast is under-estimated by about 1.6-fold, and that shortfall is where the quantitative anchor comparison failed. Second, binding affinity governs rebound height, and the labelled range spans an order of magnitude. At the

lower labelled value ($K_a \approx 10^9 \text{ M}^{-1}$) the predicted peak at the dose-aligned non-ESRD scenario, 1.08 nmol/L, falls within the observed $1.7 \pm 1.3 \text{ nmol/L}$ but below its mean; at the upper labelled value (10^{10} M^{-1}) the same scenario gives 0.36 nmol/L, a 4.7-fold under-prediction, and the Digibind value ($3.4 \times 10^{11} \text{ M}^{-1}$) gives 0.05 nmol/L, 32.5-fold low [4, 20, 21, 22, 29]. Third, over the horizon examined the label dose is sufficient at the level of concentration. Peak free digoxin stayed between 0.46 and 0.80 nmol/L across the strata, against a treatment-trigger concentration of 2.6 nmol/L, and the threshold was crossed only at sub-neutralising doses, and only at the lower end of the labelled affinity range. What changes with renal function is not whether free digoxin is suppressed but how long the suppression is held.

Comparison with previous work. Bracken and colleagues built the model class we extend, and both of their qualitative observations are reproduced here: rebound persisted at four times the label dose, and a sub-neutralising dose still drove free digoxin to a deep nadir [23]. What their model could not carry is the antibody's own disposition and its renal dependence, which are what set the duration of suppression. Their model did reproduce a rebound, but that rebound comes from the tissue redistribution term, not the antibody term, which enters as a constant removal carrying neither a time course nor a renal dependence. Removing the antibody's own disposition therefore removes the mechanism that ends the suppression, and the two representations differ in kind, not in degree. The model also matches the label's terminal half-lives (1.83 d normal, 3.55 d anuric) and the 6.8 h distribution phase, with a converged solution. A second implication concerns affinity. That a single order of magnitude in K_a moves the predicted peak several-fold places the labelled affinity range, and the gap between two products differing by one to two orders of magnitude, among the quantities that decide whether a rebound is numerically important [20, 22]. The clinical literature fits an antibody effect that wanes with the antibody, not a permanent sink. Complex elimination is slower than that of free Fab [16, 36], complexes are retained in renal failure [37], plasma exchange has been used to remove Fab and its bound drug when rebound was severe [38, 39], and the most recent practice reports describe a shift to smaller, titrated doses [8]. The renal gradient found here is the model counterpart of those observations.

Limitations. First, plasma protein binding is not modelled as a distributional restriction: the tissue-driving term uses the non-Fab-bound plasma concentration, and the small protein-bound fraction (about 25% by label) is declared, not applied [24]. Second, the Fab half-life is internally inconsistent across sources: the label's 15 h and the reported systemic clearance of 0.32 mL/min/kg with a 0.3 L/kg volume cannot both hold; the model implies 10.83 h, and forcing the label's 15 h moved the rebound time 24% later and roughly halved the peak [4, 16]. Third, affinity dominates the rebound peak and cannot be tuned away within the range the literature supports; this is structural, not a nuisance parameter. Fourth, the quantitative anchor comparison failed, and the failure is reported as it stands. The anchor cohort did not report renal function for its non-ESRD subgroup, so the proxy stratum for that subgroup cannot be pinned down; the sensitivity of the result to that choice is quantified, and substituting an alternative proxy restores agreement [11]. The primary endpoint was also re-specified before any refitting, from threshold crossing to the time to post-nadir maximum, because the threshold asks whether free digoxin returns to the level that triggered treatment,

which after adequate neutralisation it cannot; crossing is a conditional secondary endpoint only. Fifth, oral bioavailability is handled uniformly, with the same value in the model input and the vial-count formula, so the two cannot drift apart [4]. Sixth, Fab allometric scaling is animal-derived and used only for scaling [17]. Seventh, no paediatric stratification was performed, for lack of parameters [40]. Beyond these, the fixed-clearance comparator is our own reconstruction, calibrated to our model's nadir at normal renal function, not a re-implementation of the published PBPK code [23]. The treatment-trigger concentration of 2.6 nmol/L comes from one small study and is not an established threshold [9]; assay interference from ovine Fab, and the value of measuring free and total digoxin together, are further caveats on any comparison with measured free-drug data [41, 42].

Interpretation. We do not compute an optimal dose and draw no dosing recommendation; the timing question stays where Bracken and colleagues left it, now inside a framework where it can be posed quantitatively. What the model supports is narrower. The current single dose held free digoxin below the treatment-trigger concentration in every renal stratum, so the case for changing it does not rest on the exposure it produces. The duration of that suppression, by contrast, is a property of the antibody–complex system, not of the dose, and it varied more than threefold across renal function. Reports of severe rebound after single-dose strategies, including a recent death after a strategy based on reported ingested amount [43], fit a quantity the burden-based dose definition does not contain. Free digoxin can be measured alongside total digoxin in practice [41], so the renal gradient predicted here is testable prospectively.

Acknowledgements The author has no individuals or organisations to acknowledge.

Author contributions (CRediT) Tian-Yu Wang: Conceptualization; Methodology; Software; Validation; Formal analysis; Investigation; Data curation; Visualization; Writing – original draft; Writing – review & editing.

Declarations

Funding

No funding was received for conducting this study.

Competing interests

The author has no relevant financial or non-financial interests to disclose.

Ethics

This study used previously published human pharmacokinetic parameters and numerical simulation. It did not involve human participants or animals, and no ethics approval or informed consent was required.

Data availability

All model parameters are taken from the published sources cited in the manuscript. The simulation outputs and the model source code that support the findings of this study are

openly available at <https://github.com/GustaveKateb0709/digoxin-fab-rebound-kinetics>; every number reported here can be traced to a named field in the archived result files.

References

1. Smith TW, Haber E, Yeatman L, Butler VP Jr (1976) Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *New England Journal of Medicine* 294:797-800. <https://doi.org/10.1056/nejm197604082941501>
2. Lapostolle F, Borron SW, Verdier C, Taboulet P, Guerrier G, Adnet F et al (2008) Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Critical Care Medicine* 36:3014-3018. <https://doi.org/10.1097/ccm.0b013e31818b341c>
3. Flanagan RJ, Jones AL (2004) Fab antibody fragments: some applications in clinical toxicology. *Drug Safety* 27:1115-1133. <https://doi.org/10.2165/00002018-200427140-00004>
4. Digoxin Immune Fab (Ovine) [prescribing information] (2026) DigiFab, digoxin immune Fab (ovine) for intravenous injection only – lyophilized powder for solution. DailyMed / U.S. National Library of Medicine (SPL setid 49ee0505-77a0-1ff4-e063-6294a90a410e). <https://dailymed.nlm.nih.gov/dailymed/services/v2/spls/49ee0505-77a0-1ff4-e063-6294a90a410e.xml> Accessed 23 September 2026
5. Chan BSH, Buckley NA (2014) Digoxin-specific antibody fragments in the treatment of digoxin toxicity. *Clinical Toxicology* 52:824-836. <https://doi.org/10.3109/15563650.2014.943907>
6. Hack JB, Wingate S, Zolty R, Rich MW, Hauptman PJ (2025) Expert consensus on the diagnosis and management of digoxin toxicity. *The American Journal of Medicine* 138:25-33.e14. <https://doi.org/10.1016/j.amjmed.2024.08.018>
7. Nordin MP, Cox JF, Love BL, Mefford B (2026) Evaluation of digoxin dosing and therapeutic drug monitoring in adult patients receiving continuous venovenous hemodiafiltration. *Therapeutic Advances in Drug Safety* 17:20420986261481989. <https://doi.org/10.1177/20420986261481989>
8. Chan BS, Jeong J, Cairns R, Buckley NA (2026) Adherence to evidence-based practice in the treatment of digoxin poisoning in New South Wales, Australia. *British Journal of Clinical Pharmacology* 92:969-979. <https://doi.org/10.1002/bcp.70326>
9. Chan BS, Isbister GK, Chiew A, Isoardi K, Buckley NA (2022) Clinical experience with titrating doses of digoxin antibodies in acute digoxin poisoning. (ATOM-6). *Clinical Toxicology* 60:433-439. <https://doi.org/10.1080/15563650.2021.1968422>
10. Butler VP Jr, Schmidt DH, Smith TW, Haber E, Raynor BD, Demartini P (1977) Effects of sheep digoxin-specific antibodies and their Fab fragments on digoxin pharmacokinetics in dogs. *Journal of Clinical Investigation* 59:345-359. <https://doi.org/10.1172/jci108647>
11. Ujhelyi MR, Robert S, Cummings DM, Colucci RD, Green PJ, Sailstad J et al (1993) Influence of digoxin immune Fab therapy and renal dysfunction on the disposition of total

and free digoxin. *Annals of Internal Medicine* 119:273-277. <https://doi.org/10.7326/0003-4819-119-4-199308150-00004>

12. Mehta RN, Mehta NJ, Gulati A (2002) Late rebound digoxin toxicity after digoxin-specific antibody fab fragments therapy in anuric patient. *The Journal of Emergency Medicine* 22:203-206. [https://doi.org/10.1016/s0736-4679\(01\)00465-6](https://doi.org/10.1016/s0736-4679(01)00465-6)

13. Abdel Jalil M, Abdullah N, Alsous M, Abu-Hammour K (2021) Population pharmacokinetic studies of digoxin in adult patients: a systematic review. *European Journal of Drug Metabolism and Pharmacokinetics* 46:325-342. <https://doi.org/10.1007/s13318-021-00672-6>

14. Zhang Y, Liu Y, He H, Hao K (2026) Physiologically based pharmacokinetic modeling of digoxin in adult and pediatric patients with heart failure. *Pharmaceutics* 18:112. <https://doi.org/10.3390/pharmaceutics18010112>

15. Neuhoff S, Yeo KR, Barter Z, Jamei M, Turner DB, Rostami-Hodjegan A (2013) Application of permeability-limited physiologically-based pharmacokinetic models: Part I-digoxin pharmacokinetics incorporating P-glycoprotein-mediated efflux. *Journal of Pharmaceutical Sciences* 102:3145-3160. <https://doi.org/10.1002/jps.23594>

16. Ujhelyi MR, Robert S (1995) Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clinical Pharmacokinetics* 28:483-493. <https://doi.org/10.2165/00003088-199528060-00006>

17. Grene-Lerouge NAM, Bazin-Redureau MI, Debray M, Scherrmann JMG (1996) Interspecies scaling of clearance and volume of distribution for digoxin-specific Fab. *Toxicology and Applied Pharmacology* 138:84-89. <https://doi.org/10.1006/taap.1996.0101>

18. Ujhelyi MR, Robert S, Cummings DM, Colucci RD, Sailstad JM, Vlasses PH et al (1993) Disposition of digoxin immune fab in patients with kidney failure. *Clinical Pharmacology and Therapeutics* 54:388-394. <https://doi.org/10.1038/clpt.1993.165>

19. Renard C, Grene-Lerouge N, Beau N, Baud F, Scherrmann JM (1997) Pharmacokinetics of digoxin-specific Fab: effects of decreased renal function and age. *British Journal of Clinical Pharmacology* 44:135-138. <https://doi.org/10.1046/j.1365-2125.1997.00654.x>

20. Allen G (1996) The affinity of binding of digoxin to ovine anti-digoxin Fab (DIGIBIND™)* preparations. *Biologicals* 24:19-24. <https://doi.org/10.1006/biol.1996.0002>

21. Smith TW, Butler VP Jr, Haber E (1970) Characterization of antibodies of high affinity and specificity for the digitalis glycoside digoxin. *Biochemistry* 9:331-337. <https://doi.org/10.1021/bi00804a020>

22. Dijkman MA, Gresnigt FMJ, de Lange DW (2024) Digoxin-specific antibodies: a novel dosing strategy. *Netherlands Heart Journal* 32:70-73. <https://doi.org/10.1007/s12471-023-01814-y>

23. Bracken LM, Chan BSH, Buckley NA (2019) Physiologically based pharmacokinetic modelling of acute digoxin toxicity and the effect of digoxin-specific antibody fragments. *Clinical Toxicology* 57:117-124. <https://doi.org/10.1080/15563650.2018.1503288>

24. Lanoxin (digoxin) tablets [prescribing information] (2024) LANOXIN (digoxin) tablets, for oral use. DailyMed / U.S. National Library of Medicine (SPL setid d91e3646-4c63-4512-ab22-db39c085c4dc). <https://dailymed.nlm.nih.gov/dailymed/services/v2/spls/d91e3646-4c63-4512-ab22-db39c085c4dc.xml> Accessed 23 September 2026
25. Yukawa E, Suematu F, Yukawa M, Minemoto M, Ohdo S, Higuchi S et al (2001) Population pharmacokinetics of digoxin in Japanese patients: a 2-compartment pharmacokinetic model. *Clinical Pharmacokinetics* 40:773-781. <https://doi.org/10.2165/00003088-200140100-00005>
26. Salcedo-Mingoarranz AL, Medellín-Garibay SE, Barcia-Hernández E, García-Díaz B (2023) Population pharmacokinetics of digoxin in nonagenarian patients: optimization of the dosing regimen. *Clinical Pharmacokinetics* 62:1725-1738. <https://doi.org/10.1007/s40262-023-01313-8>
27. Iisalo E (1977) Clinical pharmacokinetics of digoxin. *Clinical Pharmacokinetics* 2:1-16. <https://doi.org/10.2165/00003088-197702010-00001>
28. Steiness E, Waldorff S, Hansen PB (1982) Renal digoxin clearance: Dependence on plasma digoxin and diuresis. *European Journal of Clinical Pharmacology* 23:151-154. <https://doi.org/10.1007/BF00545970>
29. Phebra Pty Ltd (2014) DigiFab (digoxin-specific antibody fragment F(Ab) (ovine)) powder for injection: product information (AusPAR attachment 1). Therapeutic Goods Administration (Australia), AusPAR PM-2012-03387-1-3, final 5 May 2014. <https://www.tga.gov.au/sites/default/files/auspar-digoxin-specific-140505-pi.pdf> Accessed 23 September 2026
30. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2024) KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International* 105:S117-S314. <https://doi.org/10.1016/j.kint.2023.10.018>
31. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-41. <https://doi.org/10.1159/000180580>
32. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clinical Practice* 120:c179-c184. <https://doi.org/10.1159/000339789>
33. Petzold L (1983) Automatic selection of methods for solving stiff and nonstiff systems of ordinary differential equations. *SIAM Journal on Scientific and Statistical Computing* 4:136-148. <https://doi.org/10.1137/0904010>
34. Virtanen P, Gommers R, Oliphant TE et al (2020) SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nature Methods* 17:261-272. <https://doi.org/10.1038/s41592-019-0686-2>
35. McNally K, Cotton R, Loizou GD (2011) A workflow for global sensitivity analysis of PBPK models. *Frontiers in Pharmacology* 2:31. <https://doi.org/10.3389/fphar.2011.00031>

36. Schaumann W, Kaufmann B, Neubert P, Smolarz A (1986) Kinetics of the fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *European Journal of Clinical Pharmacology* 30:527-533. <https://doi.org/10.1007/bf00542410>
37. Zdunek M, Mitra A, Mokrzycki MH (2000) Plasma exchange for the removal of digoxin-specific antibody fragments in renal failure: Timing is important for maximizing clearance. *American Journal of Kidney Diseases* 36:177-183. <https://doi.org/10.1053/ajkd.2000.8291>
38. Preston H, Cannon E, Watson S (2024) Plasma exchange for the management of digoxin toxicity in an individual with an acute kidney injury: A case report. *Journal of the Royal College of Physicians of Edinburgh* 54:55-58. <https://doi.org/10.1177/14782715241239372>
39. Williams JM, Reddy P (2025) Digoxin toxicity in renal failure: resolution with plasma exchange after Fab therapy failure. *Cureus* 17:e96841. <https://doi.org/10.7759/cureus.96841>
40. Abdel Jalil MH, Abdullah N, Alsous MM, Saleh M, Abu-Hammour K (2020) A systematic review of population pharmacokinetic analyses of digoxin in the paediatric population. *British Journal of Clinical Pharmacology* 86:1267-1280. <https://doi.org/10.1111/bcp.14272>
41. Eyer F, Steimer W, Müller C, Zilker T (2010) Free and total digoxin in serum during treatment of acute digoxin poisoning with Fab fragments: case study. *American Journal of Critical Care* 19:391. <https://doi.org/10.4037/ajcc2009227>
42. Rainey PM (1989) Effects of digoxin immune Fab (ovine) on digoxin immunoassays. *American Journal of Clinical Pathology* 92:779-786. <https://doi.org/10.1093/ajcp/92.6.779>
43. Cole JB, Pepin LC, Oakland CL, Bilden EF (2025) Should digoxin immune fab be administered based solely on reported ingested amount in acute digoxin poisoning? *The American Journal of Emergency Medicine* 89:309.e3-309.e6. <https://doi.org/10.1016/j.ajem.2025.01.038>

Figure

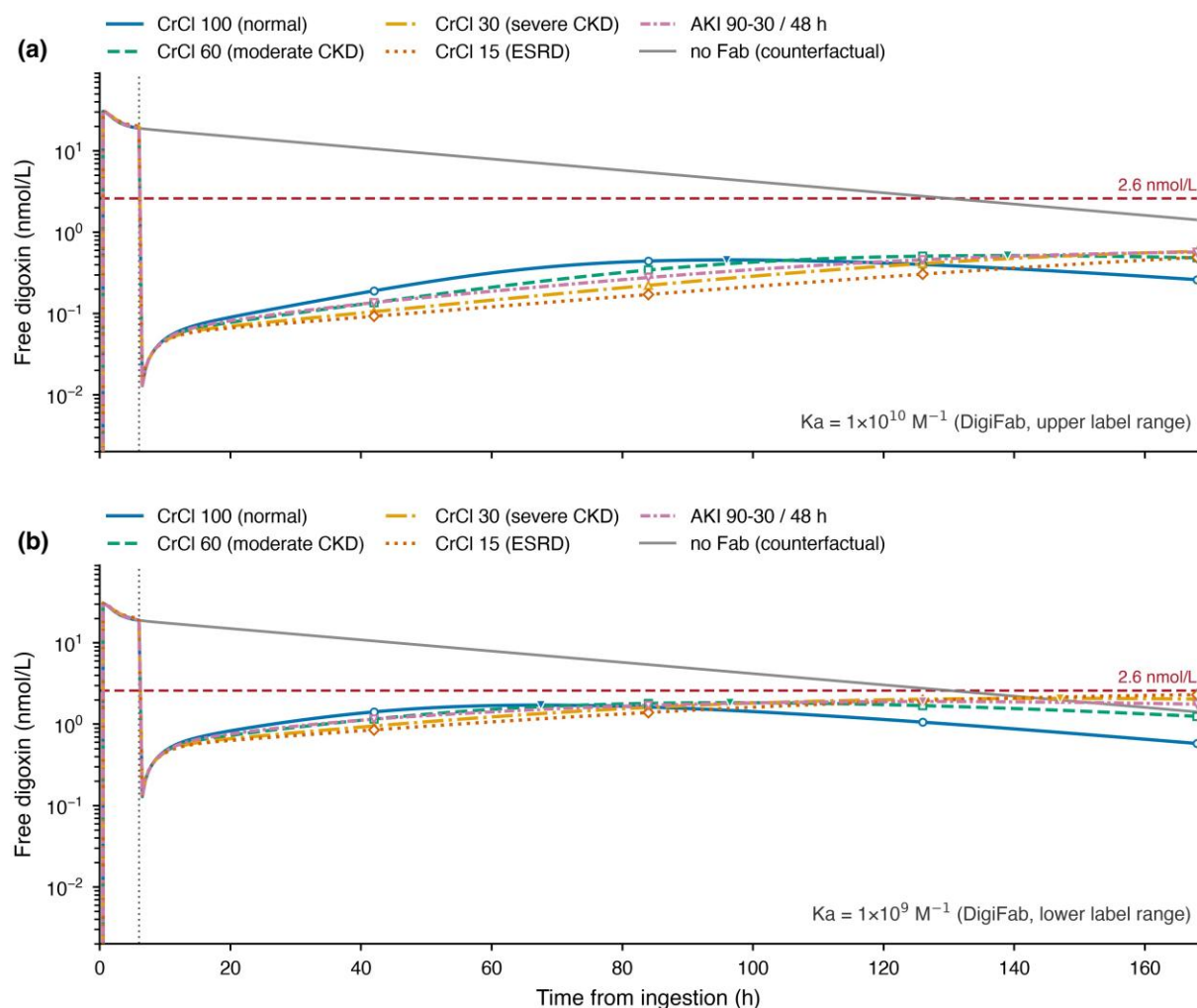


Fig 1 Free digoxin after a single label dose of Fab in four renal strata and in AKI, at $K_a = 1 \times 10^{10} \text{ M}^{-1}$ (a) and $1 \times 10^9 \text{ M}^{-1}$ (b). The vertical axis is the free, non-Fab-bound central concentration, log scale; time runs from ingestion, with the bolus at 6 h. The legend gives each line style: CrCl 100 normal, CrCl 60 moderate CKD, CrCl 30 severe CKD and CrCl 15 ESRD (solid, dashed, dash-dot and dotted lines), AKI 90-30 / 48 h (broken line) and no Fab (upper unbroken line). Filled triangles mark t_{peak} , the primary endpoint, the time from Fab to the maximum after the nadir, the anchor cohort's operational definition of rebound [11]. The dashed line is the 2.6 nmol/L ATOM-6 criterion [9], a conditional secondary endpoint only

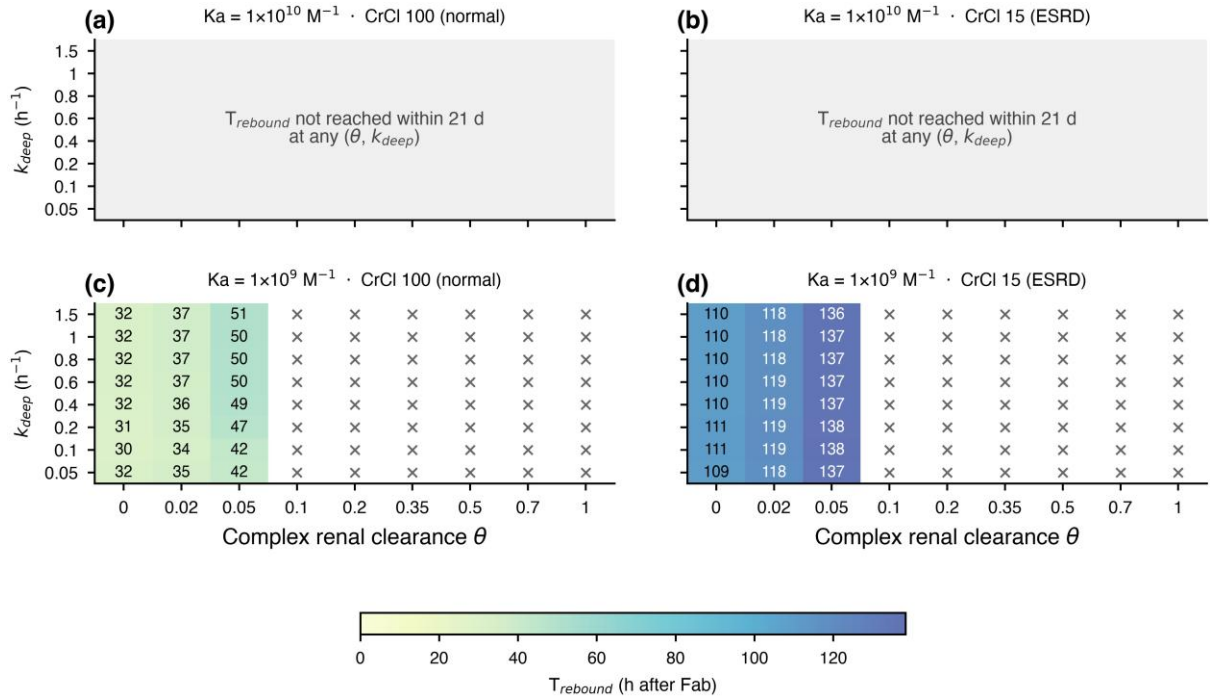


Fig 2 Time to re-cross the 2.6 nmol/L threshold after Fab on the two parameter axes the literature does not identify, the complex renal clearance fraction θ and the deep-tissue exchange rate k_{deep} . Panels are $K_a = 1 \times 10^{10} \text{ M}^{-1}$ with normal renal function (a) and ESRD (b), and $K_a = 1 \times 10^9 \text{ M}^{-1}$ with normal renal function (c) and ESRD (d). Each filled cell gives $T_{rebound}$, the hours from Fab to the first upward crossing of the 2.6 nmol/L ATOM-6 criterion [9], read against the shared scale bar; a cross means no crossing within the 21 d horizon. The two upper panels are unfilled: no crossing occurs at any (θ, k_{deep}) , including at $\theta = 0$. Neither axis was fitted, θ being provisional and k_{deep} an assumption, and both are scanned

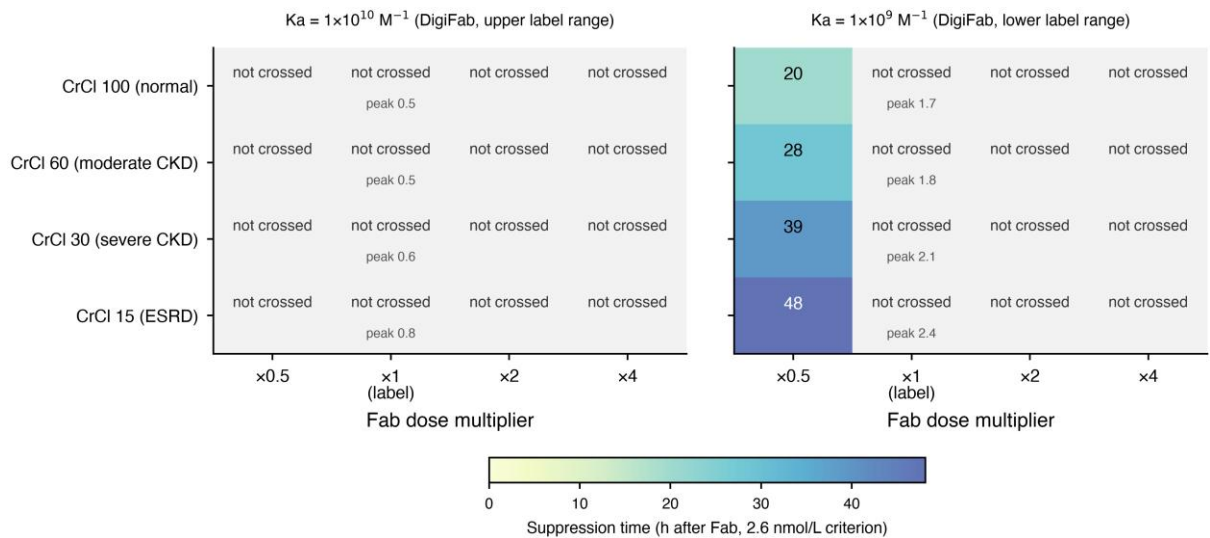


Fig 3 Threshold re-crossing by renal stratum and Fab dose multiplier, at $K_a = 1 \times 10^{10} \text{ M}^{-1}$ (left) and $K_a = 1 \times 10^9 \text{ M}^{-1}$ (right). Rows are the four stable strata of Table 1 and columns are multiples of the label Formula-1 dose [4]: $\times 0.5$, the label dose itself, $\times 2$ and $\times 4$. A filled cell gives the hours after Fab to the first upward crossing of the 2.6 nmol/L ATOM-6 criterion [9]. A cell left unfilled is marked "not crossed" within the 21 d horizon and carries the post-nadir rebound peak of that stratum at the label dose in nmol/L, which is a property of the stratum and of the affinity rather than of the multiplier. In this grid, crossing appears only at half the label dose, and only on the lower-affinity panel

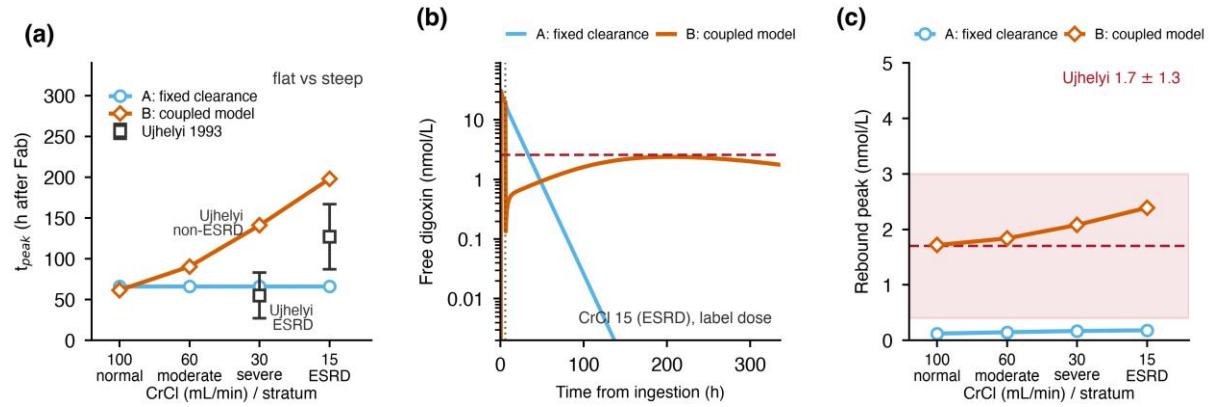
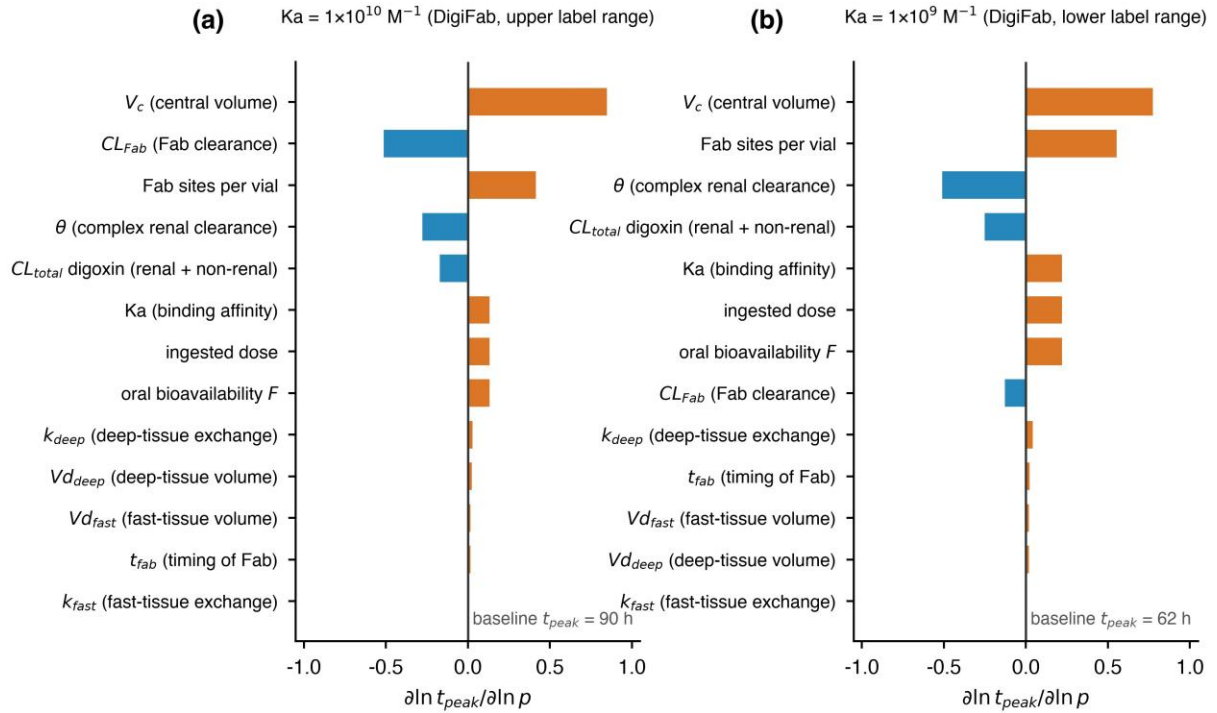
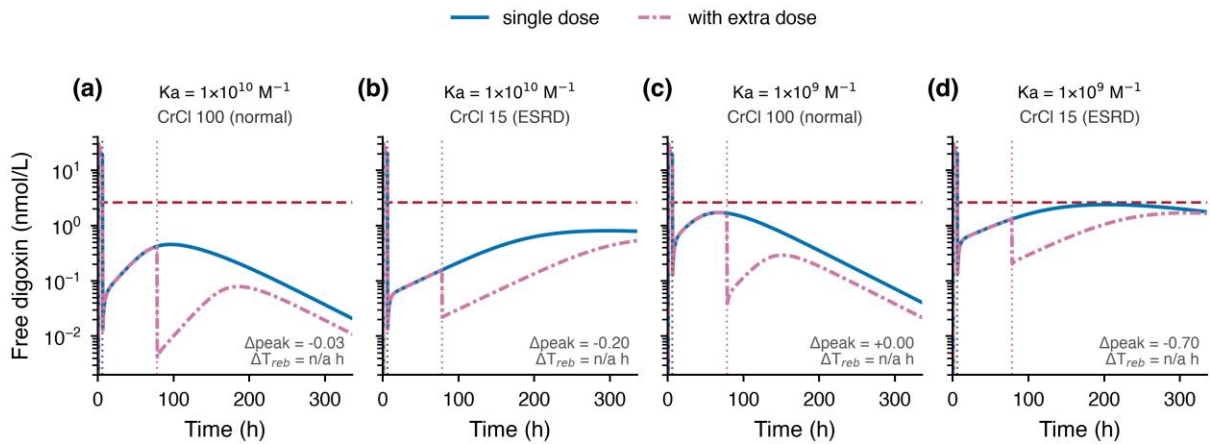


Fig 4 The published fixed-clearance model (A) against the coupled model (B), at $K_a = 1 \times 10^9 \text{ M}^{-1}$ and the label dose. The strata are plotted as categories in order of declining renal function. (a) t_{peak} by stratum, A in open circles, B in open diamonds, and the anchor subgroups [11] as open squares with ± 1 SD bars, placed at CrCl 30 and 15 because the cohort did not report its non-ESRD subgroup's renal function. A's extra clearance is calibrated once at CrCl 100 and held constant, so its profile is flat by construction, 66.0 h in every stratum, while B rises from 61.5 to 198.0 h. (b) Free digoxin after the bolus in the ESRD stratum, log scale, with the 2.6 nmol/L threshold dashed [9]. (c) Post-nadir rebound peak by stratum, with the observed 1.7 ± 1.3 nmol/L band [11] shaded

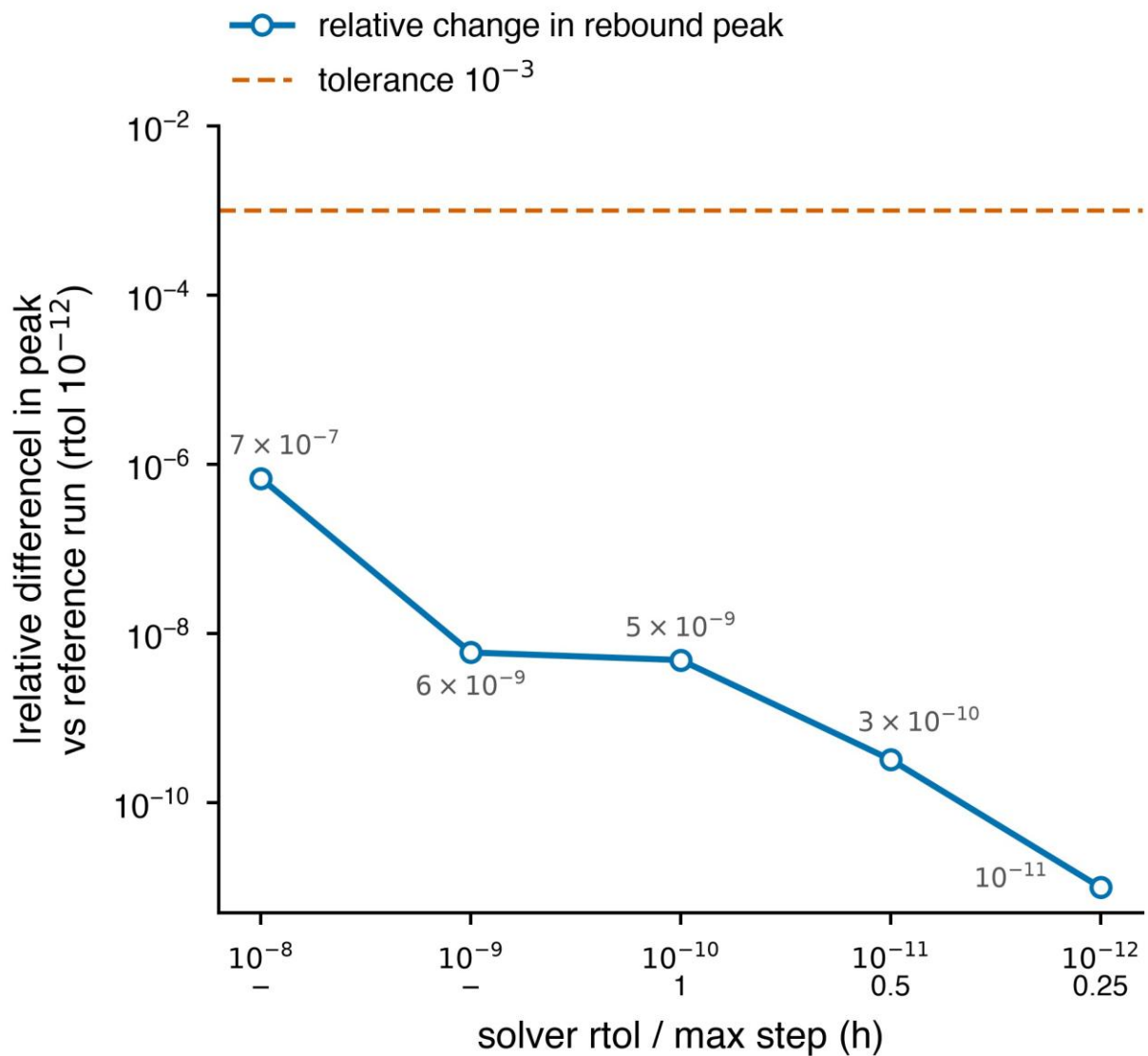


Online Resource 1 One-at-a-time sensitivity of the primary endpoint, expressed as the log–log elasticity of t_{peak} with respect to each parameter, at $K_a = 1 \times 10^{10} \text{ M}^{-1}$ (a) and $K_a = 1 \times 10^9 \text{ M}^{-1}$ (b). Each parameter was moved to 0.5 and 2 times its reference value and the elasticity is the average of the two directions, a positive value meaning a later rebound peak. Central volume ranks first at both affinities (0.85 and 0.78), the complex renal clearance fraction θ fourth at the upper affinity (–0.28) and third at the lower (–0.51), and every deep- and fast-tissue parameter lies below 0.05. Reference t_{peak} values are 90.0 h and 61.5 h



Online Resource 2 Effect of a second identical label dose 72 h after the first, at $K_a = 1 \times 10^{10} \text{ M}^{-1}$ with normal renal function (a) and ESRD (b), and at $K_a = 1 \times 10^9 \text{ M}^{-1}$ with normal renal function (c) and ESRD (d). Solid lines are the single-dose scenario, dash-dot lines the extra-dose scenario, the vertical axis is logarithmic, the dashed line is the 2.6 nmol/L ATOM-6 criterion [9], and the vertical dotted line marks 72 h. Each panel annotates the change in the

rebound peak and in T_{rebound} , the latter not applicable because no panel re-crosses the threshold. The rule was fixed in advance: T_{rebound} never preceded 72 h in any of the four scenarios, so the second dose was given nominally at 72 h in all of them



Online Resource 3 Numerical convergence of the primary endpoint. Five runs re-integrate the reference scenario at progressively tighter relative tolerances, the last three also constraining the maximum step to 1, 0.5 and 0.25 h. The vertical axis is the absolute relative difference in the post-nadir rebound peak against the tightest run, at $\text{rtol } 10^{-12}$. The largest such difference is 7×10^{-7} , against the pre-declared tolerance of 10^{-3} shown as the dashed line, and t_{peak} is 90.0 h in every run. The reference run's difference is exactly zero, which a logarithmic axis cannot show, and is drawn at the bottom of the axis