

Supplementary Information: Virtual Phase I trials predict drug induced QT prolongation from human ventricular tissue

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1 Fibroblast-dependent conductivity scaling rule

Diffuse interstitial fibrosis was introduced by randomly assigning approximately 4% of the mesh nodes to fibroblasts, consistently with histological evidence supporting a low-degree fibrotic content in adult human myocardium [1]. This value was therefore used as the baseline physiological fibrosis level in the model.

Because fibroblasts can electrically interact with neighboring cardiomyocytes through gap-junctional coupling, their local presence may alter the electrical properties of the surrounding tissue and modulate impulse propagation [2–4]. To incorporate this effect at the tissue scale, a fibroblast-dependent conductivity scaling rule was applied at the level of each finite element.

Let $\mathcal{T} = \{e\}$ denote the set of finite elements. For each element $e \in \mathcal{T}$, the local fibroblast fraction was defined as

$$f_e = \frac{n_F(e)}{n_e}, \quad (\text{S1})$$

where $n_F(e)$ is the number of fibroblast nodes in the element and n_e is the total number of nodes in the element. Since linear hexahedral elements were used, $n_e = 8$, and therefore

$$f_e = \frac{n_F(e)}{8}, \quad n_F(e) = 0, 1, \dots, 8. \quad (\text{S2})$$

Table S1: Discrete element-wise implementation of the fibroblast-dependent conductivity scaling rule. For each linear hexahedral element, the local fibroblast fraction was computed from the number of fibroblast nodes within the element. The reference cardiomyocyte conductivity was $\sigma_{\text{CM}} = 0.0023 \text{ S/cm}$, and a residual conductivity fraction $\gamma = 0.25$ was assigned to a fully fibroblastic element.

Element composition	Fibroblast fraction	Scaling factor	Conductivity retained [%]	Effective conductivity [S/cm]
0F/8CM	0.000	1.000	100.0	2.300×10^{-3}
1F/7CM	0.125	0.906	90.6	2.084×10^{-3}
2F/6CM	0.250	0.812	81.2	1.869×10^{-3}
3F/5CM	0.375	0.719	71.9	1.653×10^{-3}
4F/4CM	0.500	0.625	62.5	1.438×10^{-3}
5F/3CM	0.625	0.531	53.1	1.222×10^{-3}
6F/2CM	0.750	0.438	43.8	1.006×10^{-3}
7F/1CM	0.875	0.344	34.4	7.906×10^{-4}
8F/0CM	1.000	0.250	25.0	5.750×10^{-4}

The reference conductivity of a purely cardiomyocyte element was denoted by σ_{CM} . In the present model, the longitudinal cardiomyocyte conductivity was set to

$$\sigma_{\text{CM}} = 0.0023 \text{ S/cm}. \quad (\text{S3})$$

The presence of fibroblasts within an element was assumed to reduce the local effective conductivity according to a linear scaling law:

$$S(f_e) = 1 - (1 - \gamma)f_e, \quad (\text{S4})$$

where γ is the residual conductivity fraction assigned to a fully fibroblastic element. Accordingly, the effective conductivity of element e was computed as

$$\sigma_{\text{eff}}(e) = \sigma_{\text{CM}} S(f_e) = \sigma_{\text{CM}} [1 - (1 - \gamma)f_e]. \quad (\text{S5})$$

In this study, $\gamma = 0.25$ was used, meaning that an element composed entirely of fibroblast nodes retained one quarter of the reference cardiomyocyte conductivity. Since each hexahedral element contains eight nodes, the scaling law was implemented in discrete increments of $1/8$, yielding

$$\sigma_{\text{eff}}^{(k)} = \sigma_{\text{CM}} \left(1 - 0.75 \frac{k}{8} \right), \quad k = 0, 1, \dots, 8, \quad (\text{S6})$$

where k is the number of fibroblast nodes within the element.

Thus, elements containing only cardiomyocytes retained the reference conductivity σ_{CM} , whereas elements composed entirely of fibroblast nodes were assigned an effective conductivity equal to $0.25 \sigma_{\text{CM}}$. Intermediate configurations were obtained by linear

interpolation according to the number of fibroblast nodes within the element. The resulting element-wise scaling factor was applied to the local conductivity tensor used in the monodomain formulation.

2 Regulatory status and pharmacological class of drugs

Table S2: Drugs, pharmacological class, and high-level regulatory/commercial status. Status is reported at a high level across major regulatory markets when possible; “Active” should not be interpreted as absence of QT/TdP liability.

Drug	Pharmacological class	Regulatory/commercial status
Amiodarone	Class III antiarrhythmic (multi-ion channel blocker)	Active; QT prolongation is recognized, but TdP risk is context-dependent and lower than expected from QT prolongation alone [5, 6]
Amitriptyline	Tricyclic antidepressant (TCA)	Active; QT/TdP concern is mainly dose-, overdose-, interaction-, and susceptibility-dependent [5, 7]
Azithromycin	Macrolide antibiotic	Active; labeling and FDA communications warn about QT prolongation and potentially fatal arrhythmias in susceptible patients [8, 9]
Bepiridil	Antianginal / calcium channel blocker (multi-channel effects)	Active regionally, notably Japan; withdrawn/not marketed in several major markets because of QT/TdP liability [6, 10, 11]
Chloroquine	Antimalarial (4-aminoquinoline)	Active; QT prolongation and ventricular arrhythmia warnings apply, but “boxed QT warning” should not be used unless a specific label supports it [12, 13]
Cibenzoline	Class Ia antiarrhythmic (Na ⁺ channel blocker)	Active in selected regional markets, including Japan; not a broadly marketed FDA/EU reference compound [14]
Cisapride	Prokinetic (5-HT ₄ agonist)	Withdrawn from routine US/EU marketing; limited-access or exceptional-use pathways may exist because of QT/TdP risk [15, 16]

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Drug	Pharmacological class	Regulatory/commercial status
Dofetilide	Class III antiarrhythmic	Active; initiation/re-initiation requires inpatient ECG/renal monitoring, while REMS should not be used as the current primary qualifier [17, 18]
Flecainide	Class Ic antiarrhythmic	Active; use remains restricted by proarrhythmic risk in structural heart disease rather than market withdrawal [5]
Lidocaine	Class Ib antiarrhythmic (local anesthetic)	Active [5]
Lopinavir	Antiretroviral (HIV protease inhibitor)	Active/authorised regionally only as lopinavir/ritonavir; availability and clinical use vary substantially by market [19, 20]
Mexiletine	Class Ib antiarrhythmic	Active; availability and labelled indications vary by region [5]
Mibefradil	T-type calcium channel blocker	Withdrawn from major markets because of clinically significant drug-drug interactions and safety concerns [21]
Moxifloxacin	Fluoroquinolone antibiotic	Active; QT prolongation warning and avoidance in high-risk QT settings [22]
Ondansetron	5-HT ₃ receptor antagonist	Active; high-dose single IV 32 mg regimen withdrawn/avoided, and no single IV dose should exceed 16 mg because of dose-dependent QT prolongation [23, 24]
Propafenone	Class Ic antiarrhythmic	Active [5]
Quinidine	Class Ia antiarrhythmic	Active with limited availability in some regions; established QT/TdP liability [5, 6]
Quinine	Antimalarial	Active for restricted indications; nocturnal leg-cramp use removed/not recommended in the US; QT/TdP warnings apply [25]
Ranolazine	Antianginal (late I _{Na} blocker)	Active; dose-related QTc prolongation is labelled, although clinical proarrhythmia signal is limited in studied populations [26]
Ritonavir	Antiretroviral (HIV protease inhibitor/booster)	Active [5, 20]
Rufinamide	Antiepileptic	Active; label concern is QT shortening, not QT prolongation [27]

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Drug	Pharmacological class	Regulatory/commercial status
Saquinavir	Antiretroviral (HIV protease inhibitor)	Discontinued/withdrawn in US/EU major markets; historical labels include QT prolongation warning [28]
Sertindole	Atypical antipsychotic	Restricted/authorised only in selected markets with mandatory ECG monitoring; not FDA-approved [29]
Sotalol	Class III antiarrhythmic / β -blocker	Active; initiation/re-initiation requires ECG-based monitoring because of life-threatening proarrhythmia/TdP risk [30]
Terfenadine	Antihistamine (H_1)	Withdrawn from US/EU routine markets because of QT/TdP risk and safer alternatives [31, 32]
Toremifene	Selective estrogen receptor modulator (SERM)	Active; boxed QT prolongation warning applies [33]
Verapamil	Non-DHP calcium channel blocker	Active; QT prolongation/proarrhythmia relationship differs from high-risk I_{Kr} blockers [5]
Astemizole	Antihistamine (H_1)	Withdrawn from major markets because of QT/hERG-related arrhythmia risk [32, 34]
Ceftriaxone	Cephalosporin antibiotic (3rd gen)	Active [5]
Cilostazol	PDE3 inhibitor (antiplatelet)	Active; contraindicated in heart failure, but this is not primarily a QT/TdP regulatory restriction [5]
Clozapine	Atypical antipsychotic	Active; ANC monitoring/severe-neutropenia warnings remain, but FDA REMS has been removed [35]
Dasatinib	Tyrosine kinase inhibitor	Active [5]
Diazepam	Benzodiazepine	Active [5]
Disopyramide	Class Ia antiarrhythmic	Active; established QT/TdP liability typical of Class Ia agents [5, 6]
Donepezil	Acetylcholinesterase inhibitor	Active; QT/TdP concern is mainly susceptibility-, interaction-, and case-report-dependent [5, 36]
Droperidol	Butyrophenone antiemetic/antipsychotic	Active/restricted use; boxed QT/TdP warning and monitoring considerations apply [37]
Duloxetine	SNRI antidepressant	Active [5]
Halofantrine	Antimalarial (phenanthrene methanol)	Not marketed or highly restricted in many major markets; QT/TdP risk is clinically important [25, 38]

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Drug	Pharmacological class	Regulatory/commercial status
Haloperidol	Typical antipsychotic (butyrophenone)	Active; QT/TdP warnings are especially relevant for high dose, IV use, interactions, or susceptible patients [5, 7]
Linezolid	Oxazolidinone antibiotic	Active [5]
Loratadine	Antihistamine (H ₁)	Active; generally lower QT/TdP concern than terfenadine or astemizole [5, 32]
Methadone	Opioid analgesic / opioid-use-disorder therapy	Active; life-threatening QT prolongation and TdP warnings apply [39]
Mitoxantrone	Antineoplastic (anthracenedione)	Active; major cardiac concern is cumulative cardiomyopathy rather than primary QT/TdP liability [5]
Nifedipine	DHP calcium channel blocker	Active [5]
Nitrendipine	DHP calcium channel blocker	Active in selected non-US markets; not marketed/approved in the US [5]
Paliperidone	Atypical antipsychotic	Active [5]
Paroxetine	SSRI antidepressant	Active [5]
Pentobarbital	Barbiturate sedative-hypnotic	Active but highly controlled/restricted depending on jurisdiction and use setting [5]
Phenytoin	Antiepileptic	Active [5]
Pimozide	Typical antipsychotic (diphenylbutylpiperidine)	Active with QT-based contraindications and interaction restrictions [40]
Procainamide	Class Ia antiarrhythmic	Active, mainly injectable and with variable availability; established QT/TdP liability [5, 6]
Raltegravir	Antiretroviral (integrase inhibitor)	Active [20]
Ribavirin	Antiviral (nucleoside analogue)	Active, although clinical use has declined in several indications [5]
Risperidone	Atypical antipsychotic	Active; included among compounds used in proarrhythmia-risk benchmark sets [5, 41]
Sitagliptin	DPP-4 inhibitor (antidiabetic)	Active [5]
Solifenacin	Antimuscarinic (OAB)	Active; QT concern is context-dependent and should not be equated with market restriction [5, 16]
Sparfloxacin	Fluoroquinolone antibiotic	Withdrawn/discontinued in major markets; historical labeling and literature support QT-prolongation concern [42, 43]
Sunitinib	Tyrosine kinase inhibitor (VEGFR/PDGFR)	Active [5]

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Drug	Pharmacological class	Regulatory/commercial status
Telbivudine	Antiviral (HBV nucleoside analogue)	Discontinued/withdrawn in US/EU major markets, mainly for commercial/availability reasons rather than QT/TdP liability [44]
Terodiline	Antimuscarinic (urologic)	Withdrawn because of concentration-dependent QT prolongation and ventricular arrhythmia/TdP risk [45]
Thioridazine	Typical antipsychotic (phenothiazine)	Branded product discontinued; generic/regional availability varies; use is highly restricted by QT/TdP and sudden-death risk [46, 47]

Note. “Active” denotes that the drug remains marketed or authorised in at least one major or regional market according to available labeling/authorization sources; it does not imply low cardiac risk. “Withdrawn”, “discontinued”, and “restricted” are jurisdiction-dependent terms and should be interpreted in the specific regulatory context stated in the manuscript. QT prolongation, torsades de pointes (TdP), market withdrawal, and REMS/monitoring requirements are distinct regulatory concepts.

Caveat: Regulatory statuses are jurisdiction-dependent and time-varying; therefore, local regulatory sources should be consulted for the most reliable and up-to-date information.

3 Characteristics of the entire drug dataset

Table S3: Comparison between QT-interval prolongation of in-silico clinical trials and clinical trials for all the 67 drugs evaluated.

Drug	Dosage	C_{molar} [μM]	Protein binding	MW	QT (trial)	QT (in silico)	$\Delta\overline{QT}$	UB95%	References
Amiodarone	200 mg	2.5	96.0%	645.32	48 ms	51.5 ± 3.17 ms	3.5 ms	8.00	[48–50]
Amitriptyline	75 mg	0.0039	90–96%	277.37	-0.3 ms	0.6 ± 3.81 ms	0.9 ms	4.66	[51, 52]
Azithromycin	500 mg EV	4.5	7–51%	748.98	23 ms	21.8 ± 4.42 ms	1.2 ms	5.41	[53, 54]
Bepridil	300–500 mg	0.0315	99.7%	366.54	20 ms	20 ± 3.83 ms	0 ms	4.55	[55–57]
Chloroquine	600 mg	0.2495	61.0%	319.87	15 ms	14.9 ± 2.81 ms	0.1 ms	3.31	[58, 59]
Chlorpromazine	N/A	0.0345	90–99%	318.86	N/A	4.50 ± 2.46 ms	N/A	N/A	N/A
Cibenzoline	2–2.6 mg/kg	0.673	50–60%	380.44	26 $\pm$ 12 ms	28.9 ± 3.38 ms	2.9 ms	5.42	[60, 61]
Cisapride	40 mg	0.0026	98.0%	465.945	10 ms	13.40 ± 3.44 ms	3.4 ms	5.88	[62–64]
Diltiazem	N/A	0.1275	70–80%	414.5	N/A	-16.70 ± 2.67 ms	N/A	N/A	N/A
Dofetilide	0.5 mg	0.0018	65.0%	441.62	73.6 ms	81.7 ± 2.66 ms	8.1 ms	9.88	[65, 66]
Flecainide	200 mg	0.3	40.0%	414.3	32 ms	37.9 ± 2.08 ms	5.9 ms	7.39	[67, 68]
Lidocaine	160 mg	2.5604	70.0%	234.34	~5 ms	-1.70 ± 1.49 ms	3.3 ms	4.37	[69, 70]
Lopinavir	400 mg	0.41	98.5%	628.8	6 ms	4.2 ± 3.29 ms	1.8 ms	4.45	[71, 72]
Mexiletine	600/900 mg	2.5032	55.0%	179.25	No prolong	-2.2 ± 4.02 ms	2.2 ms	5.48	[73, 74]
Mifepradil	100 mg	0.0106	99.5%	495.28	5 $\pm$ 2 ms	5.70 ± 5.29 ms	0.7 ms	6.26	[75, 76]
Moxifloxacin	400 mg	3.5625	47.0%	401.44	15 ms	15.2 ± 2.39 ms	0.2 ms	2.83	[77, 78]
Nilotinib	N/A	0.0604	98.0%	529.52	N/A	50.9 ± 4.04 ms	N/A	N/A	N/A

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Drug	Dosage	C_{molar} [μM]	Protein binding	MW	QT (trial)	QT (in silico)	ΔQT	UB95%	References
Ondansetron	4 mg	0.3585	73.0%	293.37	11 ms	11.4 ± 3.31 ms	0.4 ms	9.82	[79, 80]
Propafenone	660 ± 105 mg/die	0.131	77–89%	341.44	30 ms	25 ± 1.49 ms	5 ms	6.07	[81]
Quinidine	400 mg	0.42145	70–95%	324.42	78.9 ± 10.8 ms	76.62 ± 4.57 ms	2.28 ms	5.56	[65, 82]
Quinine	628 mg	1.48	70–92%	324.42	12 ± 18 ms	12.1 ± 4.43 ms	0.1 ms	5.21	[83–85]
Ranolazine	1500 mg	1.9482	61–64%	428.53	13 ms	22.6 ± 3.84 ms	9.6 ms	11.8	[65, 86]
Ritonavir	100 mg	0.4369	96–99.5%	720.95	< 5 ms	4.9 ± 3.6 ms	< 5 ms	4.26	[87, 88]
Rufinamide	2779 ± 410 mg	58.4	26–34%	238.17	-8.5 ± 13.7 ms	-6.50 ± 2.99 ms	2 ms	4.34	[89]
Saquinavir	500 mg	0.213	98.0%	670.87	7–9 ms	6.10 ± 3.25 ms	0.9–2.9 ms	4.51	[90–92]
Sertindole	12 mg	0.00131	99.0%	440.93	15.1 ms	17.75 ± 3.37 ms	2.65 ms	4.89	[93, 94]
Sotalol	320 mg	14.6864	0.0%	272.35	21 ms	19.9 ± 3.93 ms	1.1 ms	4.85	[95, 96]
Terfenadine	60 mg/12h	0.016	97.0%	471.66	6 ms	8 ± 3.12 ms	2 ms	4.30	[97, 98]
Toremifene	20 mg/die	0.0263	96–99.5%	406.01	7 ms	2 ± 2.62 ms	5 ms	6.88	[99–101]
Verapamil	0.2–0.4 mg/kg	0.045	92–94%	454.6	3 ms	1.6 ± 3.06 ms	1.4 ms	4.04	[102, 103]
Astemizole	30 mg	7.77E-05	97.0%	458.61	3 ms	3.75 ± 2.82 ms	0.75 ms	3.08	[104–106]
Ceftriaxone	2 g EV	23.17	60–95%	554.59	No prolong	1.2 ± 3.26 ms	1.2 ms	4.15	[107–109]
Cilostazol	50–100 mg BID	0.128	95.0%	369.43	No prolong	0.5 ± 3.41 ms	0.5 ms	4.66	[110–112]
Clozapine	276 ± 106 mg/die	0.071	94.5%	326.18	No prolong	2.30 ± 3.53 ms	2.3 ms	4.96	[113–115]
Dasatinib	100 mg	0.041	90–97%	488.01	3 ms	1 ± 2.16 ms	2 ms	3.58	[116–118]
Diazepam	Overdosage	0.029	98.0%	284.74	No prolong	1.90 ± 4.20 ms	1.9 ms	5.46	[119–121]

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Drug	Dosage	C_{inolar} [μ M]	Protein binding	MW	QT (trial)	QT (in silico)	ΔQT	UB95%	References
Disopyramide	2mg/kg	2	65.7%	339.47	39 ms	25 $\pm$ 17.8 ms	7.2 ms	9.76	[122, 123]
Donepezil	5 mg	0.003	95.6%	379.5	0.7 ms	1.90 $\pm$ 3.96 ms	1.2 ms	4.14	[124-126]
Droperidol	4.3 mg EV	0.016	85-90%	380.44	22 ms	21 $\pm$ 3.68 ms	1 ms	4.50	[127-129]
Duloxetine	60 mg	0.016	90.0%	297.43	1 ms	0.6 $\pm$ 2.95 ms	0.4 ms	3.24	[130, 131]
Halofantrine	500 mg	0.132	60-83%	500	23 ms	18.9 $\pm$ 4.25 ms	4.1 ms	7.18	[132, 133]
Haloperidol	15 mg	0.004	90-92%	375.9	7.1 ms	6.11 $\pm$ 2.76 ms	0.99 ms	3.31	[134, 135]
Lamivudine	N/A	19.54	10-36%	229.26	N/A	-10.7 $\pm$ 2.26 ms	N/A	N/A	N/A
Linezolid	1200 mg	59.11	31.0%	337.35	-7.51 ms	-9.30 $\pm$ 4.08 ms	1.79 ms	5.34	[136-138]
Loratadine	10 mg	0.0004	97-99%	382.9	4 ms	3.2 $\pm$ 4.8 ms	0.6 ms	5.56	[139-141]
Methadone	15 mg	0.507	85.0%	309.45	10 ms	14 $\pm$ 3.86 ms	4 ms	6.79	[142-144]
Metronidazole	N/A	187	20.0%	171.15	N/A	-7.3 $\pm$ 2.21 ms	N/A	N/A	N/A
Mitoxantrone	Therapeutic	0.225	78.0%	444.52	No prolong	-1.90 $\pm$ 3.41 ms	1.9 ms	4.70	[145, 146]
Nifedipine	10 mg	0.008	92-98%	346.33	-16 ms	-12.2 $\pm$ 2.78 ms	3.8 ms	5.75	[147, 148]
Nitrendipine	20 mg	0.003	93-99%	360	-8 ms	-4.5 $\pm$ 3.10 ms	3.5 ms	5.72	[149-151]
Paliperidone	12 mg	0.069	74.0%	426.48	12.3 ms	8.50 $\pm$ 3.60 ms	3.8 ms	6.38	[152, 153]
Paroxetine	20 mg	0.014	95.0%	329.37	-1 ms	0.20 $\pm$ 2.90 ms	1.2 ms	3.76	[154-156]
Pentobarbital	30-35 mg/kg	5.171	45-70%	226.28	7 ms	2.2 $\pm$ 3.49 ms	4.8 ms	7.26	[157-160]
Phenytoin	357.5 $\pm$ 127.4 mg/die	4.36	90-95%	252.27	No prolong	-1.80 $\pm$ 2.97 ms	1.8 ms	4.16	[161-163]
Pimozide	1 mg	0.0005	99.0%	461.56	2.8 $\pm$ 12 ms	3.30 $\pm$ 3.80 ms	0.5 ms	3.72	[164-166]
Piperacillin	N/A	1378	20-30%	517.56	N/A	13.2 $\pm$ 2.9 ms	N/A	N/A	N/A
Procainamide	500 mg	18	15-25%	236.34	11 ms	4.7 $\pm$ 2.79 ms	6.3 ms	3.88	[167, 168]

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Drug	Dosage	C_{molar} [μM]	Protein binding	MW	Q_T (trial)	Q_T (in silico)	ΔQ_T	UB95%	References
Raltegravir	1600 mg	7	76.0%	444.43	-4.4 ms	-0.2 ± 2.53 ms	4.2 ms	6.81	[169–171]
Ribavirin	600 mg	27.88	0.0%	244.21	2 ms	0.9 ± 3.48 ms	1.1 ms	4.35	[172, 173]
Risperidone	6–8 mg	0.002	90.0%	410.49	3.9 ms	5.40 ± 2.84 ms	1.5 ms	3.53	[134, 174, 175]
Sitagliptin	100 mg	0.8	38.0%	407.31	2 ms	2 ± 3.46 ms	0 ms	4.10	[176, 177]
Solifenacin	10 mg	0.003	93–98%	480	2 ms	2.5 ± 3.70 ms	0.5 ms	3.91	[178, 179]
Sparfloxacin	400 mg	1.766	45% NIH/EMA	392.41	11 ms	9.4 ± 2.99 ms	1.6 ms	3.95	[180, 181]
Sunitinib	150 mg	0.013	90–95%	398.474	9.6 ms	3.6 ± 4.4 ms	6 ms	9.14	[182, 183]
Telbivudine	600 mg	19.72	3.30%	242	3.6 ms	2.3 ± 2.71 ms	1.3 ms	4.14	[184, 185]
Terodiline	88.5 mg	0.145	83%	317.9	19 ms	17.9 ± 3.18 ms	1.1 ms	4.01	[186]
Thioridazine	10 mg	0.1	95%	370.57	9 ms	10.6 ± 2.46 ms	0.7 ms	3.53	[187, 188]

The first 30 Drugs are taken from Crumb et al [189] human dataset. On the other hand, the following 37 drugs are taken from Kramer et al rat dataset [190]

4 Source- and Therapeutic-Class-Stratified Sensitivity Analyses of Model Performance

Table S4: Source-stratified performance of the 4% physiological fibrosis model. Metrics were computed separately for compounds whose ion-channel pharmacology was derived from the Crumb and Kramer datasets.

Source	N	Bias [ms]	MAE [ms]	RMSE [ms]	Mean UB95 [ms]	UB95 $\leq$ 10 ms
Crumb	27	0.77	2.41	3.22	5.74	26/27 (96.3%)
Kramer	34	-0.62	2.30	3.01	4.96	34/34 (100.0%)

Table S5: Leave-one-therapeutic-class-out sensitivity analysis of UB95-based regulatory performance in the 4% physiological fibrosis configuration. Each row reports the global metrics obtained after excluding one therapeutic class. N_{rem} indicates the number of remaining compounds. $N_{\leq 10}$ and $N_{>10}$ indicate the number of compounds with UB95 absolute prediction error below/equal to or above the 10 ms threshold, respectively. Conc. indicates concordance. Mean, median, and max refer to UB95 absolute prediction error values in milliseconds.

Class excluded	N_{rem}	$N_{\leq 10}$	$N_{>10}$	Conc. [%]	Mean	Median	Max	Outlier
Antiarrhythmic	50	49	1	98.0	5.06	4.50	12.34	Ranolazine
Antidepressant	58	57	1	98.3	5.38	4.77	12.34	Ranolazine
Antibacterial	56	55	1	98.2	5.39	4.68	12.34	Ranolazine
Calcium-channel blocker	56	55	1	98.2	5.31	4.66	12.34	Ranolazine
Antimalarial	58	57	1	98.3	5.31	4.66	12.34	Ranolazine
Prokinetic/antiemetic	59	58	1	98.3	5.22	4.66	12.34	Ranolazine
Antiviral	55	54	1	98.2	5.36	4.85	12.34	Ranolazine
Other cardiovascular	59	59	0	100.0	5.19	4.66	9.88	None
CNS-active	57	56	1	98.2	5.30	4.66	12.34	Ranolazine
Antipsychotic	53	52	1	98.1	5.45	4.70	12.34	Ranolazine
Antihistamine	58	57	1	98.3	5.35	4.68	12.34	Ranolazine
Antineoplastic/endocrine	57	56	1	98.2	5.25	4.66	12.34	Ranolazine
Other	58	57	1	98.3	5.32	4.68	12.34	Ranolazine
Urologic	59	58	1	98.3	5.35	4.70	12.34	Ranolazine

5 QT interval measurement

In clinical practice, the QT interval is measured from the onset of ventricular depolarization to the end of ventricular repolarization, usually defined as the point at which

the T wave returns to the isoelectric line. In the present framework, the reconstructed signal represents a pseudo-ECG obtained from ventricular tissue only. No atrial activity or pre-ventricular electrical segment was modeled. Therefore, the pseudo-ECG trace starts at the first simulated instant of ventricular excitation. This first time point represents the earliest available temporal reference for ventricular depolarization and was operationally defined as $QRS_{onset} = t_0 = 0$ ms for all simulations. Since no electrical activity preceding ventricular activation exists in the simulated domain, selecting an earlier onset is not possible, whereas selecting a later point would artificially exclude part of the depolarization phase from the QT interval. The same definition of t_0 was applied identically to control and drug-treated simulations.

QT measurement was performed on the final simulated cardiac cycle, corresponding to the last 800-ms beat of the pacing protocol, consistent with the imposed BCL. No additional signal filtering was required, because the pseudo-ECGs were generated under controlled numerical conditions and showed clearly identifiable depolarization and repolarization phases across all analyzed simulations.

The end of the QT interval was identified using an automated tangent-based method. This approach was adopted to ensure reproducible QT measurements across all virtual patients, drugs, and concentration levels, avoiding operator-dependent variability associated with manual annotation [191, 192]. The tangent method is based on the identification of the steepest downslope of the T wave during ventricular repolarization. A tangent line is then constructed at this point, and the intersection between this tangent and the isoelectric baseline is taken as the end of the T wave, T_{end} [193].

In the present implementation, the T-wave peak was first identified using an automated peak-detection procedure to initialize the repolarization downslope search window. This step was used only to define the starting point of the segment in which the tangent method was applied, and did not directly determine T_{end} . Starting from the T-wave peak, the subsequent pseudo-ECG segment was analyzed to identify the point of maximum downslope, from which the tangent line was constructed.

The isoelectric baseline was defined as the zero reference level of the reconstructed pseudo-ECG, consistently with the reference level used in the numerical signal reconstruction. This choice was consistent with the pseudo-ECG formulation, in which the reconstructed signal is expressed relative to a zero reference potential. Therefore, T_{end} was computed as the intersection between the tangent line and the baseline.

The resulting T_{end} was accepted only if the tangent-baseline intersection occurred within the analyzed cardiac cycle and after the depolarization phase. In the present dataset, all analyzed pseudo-ECG traces satisfied these validity criteria, and no trace was excluded from the QT analysis.

The QT interval was then computed as:

$$QT = T_{end} - t_0. \quad (S7)$$

The same tangent-based procedure was applied identically to control and drug-treated simulations. Therefore, the endpoint of interest was not the absolute reproduction of clinical ECG morphology, but the relative change in QT duration induced by drug administration under the same measurement conditions.

The complete pseudo-ECG reconstruction and QT-measurement pipeline was implemented as a fixed deterministic procedure and applied uniformly to all virtual patients, compounds, and drug conditions. Thus, the digital QT endpoint was generated without operator-dependent annotation or compound-specific adjustment. Model parameters were derived from physiological assumptions, literature data, or predefined numerical settings, and were not adjusted to improve agreement with clinical QT/QTc prolongation.

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