

# Online supplementary content

Drug interactions in hospital prescriptions in Denmark: Prevalence and associations with adverse outcome

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**Table S1. Prevalence of potential drug-drug interactions based on recommendation and documentation level.**

Unique drug combinations (upper cells) and prevalence (lower cells) of pDDIs by management recommendation and documentation level. Values are N (%).

Recommendation level	Documentation level				Total
	Well documented	Documented	Limited documented	Poorly documented	
1: Discouraged	25 (17)	70 (48)	23 (16)	28 (19)	146 (3)
	8,160 (45)	5,918 (33)	3,477 (19)	2,133 (12)	18,192 (3)
2: Dose adjustment	173 (17)	540 (54)	74 (7)	218 (22)	1,005 (18)
	8,1407 (55)	91,096 (61)	3,599 (2)	23,730 (16)	148,455 (23)
3: Staggered ingestion	105 (46)	86 (38)	21 (9)	14 (6)	226 (4)
	81,050 (89)	12,129 (13)	2,744 (3)	488 (1)	90,662 (14)
4: Precautions	304 (17)	834 (48)	161 (9)	443 (25)	1,742 (31)
	16,3097 (31)	468,888 (88)	85,764 (16)	123,792 (23)	532,066 (81)
5: No action needed	259 (10)	1,755 (69)	230 (9)	283 (11)	2,527 (45)
	14,1733 (30)	399,115 (85)	216,539 (46)	170,043 (36)	470,956 (71)
Total	866 (12)	3,285 (58)	509 (9)	986 (17)	5,646
	28,8210 (44)	604,999 (92)	246,771 (37)	234,205 (36)	659,525

**Table S2. Drugs involved in discouraged drug pairs.**

Drugs used by less than 5 patients were omitted to avoid privacy issues.

Drug name	ATC	Discouraged-pDDIs (N)	Pairs (N)	Discouraged-pDDIs involving drug (%)	Admissions with discouraged-pDDIs (N)	Admissions with drug (N)	Admissions with discouraged-pDDIs (%)	Patients with discouraged-pDDI (N)	Patients with drug (N)	Patients with discouraged-pDDI (%)	Total admissions (N)	Total patients (N)	Patients overall (%)	Admissions overall (%)
Erythromycin	J01FA01	8	860	0.93	1573	5665	27.77	1461	5001	29.21	28862 27	94547 5	0.53	0.2
Rifabutin	J04AB04	2	224	0.89	25	101	24.75	10	46	21.74	28862 27	94547 5	0	0
Ketoconazole	D01AC08	6	753	0.8	644	3158	20.39	320	1513	21.15	28862 27	94547 5	0.16	0.11
Diclofenac	S01BC03	1	370	0.27	53	313	16.93	13	177	7.34	28862 27	94547 5	0.02	0.01
Clarithromycin	J01FA09	14	1086	1.29	4022	25792	15.59	3338	21008	15.89	28862 27	94547 5	2.22	0.89
Paroxetine	N06AB05	4	832	0.48	1206	8733	13.81	408	2707	15.07	28862 27	94547 5	0.29	0.3
Domperidone	A03FA03	1	1009	0.1	2872	23213	12.37	2028	10571	19.18	28862 27	94547 5	1.12	0.8
Isocarboxazid	N06AF01	4	400	1	90	789	11.41	36	249	14.46	28862 27	94547 5	0.03	0.03
Warfarin	B01AA03	16	1202	1.33	12570	12165 3	10.33	8791	42101	20.88	28862 27	94547 5	4.45	4.21
Diclofenac	D11AX18	1	289	0.35	18	197	9.14	6	87	6.9	28862 27	94547 5	0.01	0.01
Imatinib	L01XE01	1	491	0.2	139	1543	9.01	44	337	13.06	28862 27	94547 5	0.04	0.05
Etoricoxib	M01AH05	1	216	0.46	9	106	8.49	6	51	11.76	28862 27	94547 5	0.01	0
Sirolimus	L04AA10	3	434	0.69	168	2085	8.06	30	233	12.88	28862 27	94547 5	0.02	0.07

<b>Ketoconazole</b>	J02AB02	2	248	0.81	12	158	7.59	9	75	12	28862 27	94547 5	0.01	0.01
<b>Phenprocoumon</b>	B01AA04	2	542	0.37	146	1985	7.36	97	649	14.95	28862 27	94547 5	0.07	0.07
<b>Pravastatin</b>	C10AA03	1	732	0.14	371	5193	7.14	114	1518	7.51	28862 27	94547 5	0.16	0.18
<b>Ciclosporin</b>	L04AD01	5	819	0.61	681	9595	7.1	193	2257	8.55	28862 27	94547 5	0.24	0.33
<b>Clonidine</b>	N02CX02	3	982	0.31	806	11522	7	303	7371	4.11	28862 27	94547 5	0.78	0.4
<b>Piroxicam</b>	M02AA07	1	401	0.25	27	387	6.98	13	232	5.6	28862 27	94547 5	0.02	0.01
<b>Tizanidine</b>	M03BX02	3	703	0.43	321	4744	6.77	194	1244	15.59	28862 27	94547 5	0.13	0.16
<b>Dronedarone</b>	C01BD07	1	307	0.33	59	910	6.48	32	325	9.85	28862 27	94547 5	0.03	0.03
<b>Tenoxicam</b>	M01AC02	1	271	0.37	15	246	6.1	5	105	4.76	28862 27	94547 5	0.01	0.01
<b>Diclofenac</b>	M02AA15	1	443	0.23	24	433	5.54	16	253	6.32	28862 27	94547 5	0.03	0.02
<b>Voriconazole</b>	J02AC03	3	734	0.41	192	3542	5.42	49	1418	3.46	28862 27	94547 5	0.15	0.12
<b>Itraconazole</b>	J02AC02	2	578	0.35	53	1149	4.61	38	532	7.14	28862 27	94547 5	0.06	0.04
<b>Fluconazole</b>	J02AC01	2	1318	0.15	3802	88426	4.3	2929	50842	5.76	28862 27	94547 5	5.38	3.06
<b>Ibuprofen</b>	M02AA13	1	290	0.34	6	148	4.05	5	94	5.32	28862 27	94547 5	0.01	0.01
<b>Rifampicin, Pyrazinamide, Ethambutol and Isoniazid</b>	J04AM06	4	303	1.32	12	328	3.66	7	203	3.45	28862 27	94547 5	0.02	0.01
<b>Nabumetone</b>	M01AX01	1	493	0.2	27	759	3.56	18	339	5.31	28862 27	94547 5	0.04	0.03
<b>Simvastatin and Ezetimibe</b>	C10BA02	2	284	0.7	10	293	3.41	8	101	7.92	28862 27	94547 5	0.01	0.01

<b>Terbinafine</b>	D01BA02	5	631	0.79	57	1685	3.38	31	912	3.4	28862 27	94547 5	0.1	0.06
<b>Carbamazepine</b>	N03AF01	8	873	0.92	337	10396	3.24	178	3167	5.62	28862 27	94547 5	0.33	0.36
<b>Terbinafine</b>	D01AE15	5	848	0.59	211	6839	3.09	144	4481	3.21	28862 27	94547 5	0.47	0.24
<b>Diclofenac, combinations</b>	M01AB55	1	546	0.18	37	1371	2.7	22	598	3.68	28862 27	94547 5	0.06	0.05
<b>Etodolac</b>	M01AB08	1	847	0.12	370	14021	2.64	251	9338	2.69	28862 27	94547 5	0.99	0.49
<b>Azathioprine</b>	L04AX01	1	896	0.11	315	12493	2.52	139	3640	3.82	28862 27	94547 5	0.38	0.43
<b>Ritonavir</b>	J05AE03	5	590	0.85	76	3029	2.51	47	792	5.93	28862 27	94547 5	0.08	0.1
<b>Amitriptyline</b>	N06AA09	3	1114	0.27	902	36127	2.5	376	12365	3.04	28862 27	94547 5	1.31	1.25
<b>Emtricitabine, tenofovir disoproxil, elvitegravir and cobicistat</b>	J05AR09	4	232	1.72	5	209	2.39	5	93	5.38	28862 27	94547 5	0.01	0.01
<b>Fluoxetine</b>	N06AB03	2	875	0.23	215	10164	2.12	150	3450	4.35	28862 27	94547 5	0.36	0.35
<b>Colchicine</b>	M04AC01	1	779	0.13	165	8144	2.03	93	3728	2.49	28862 27	94547 5	0.39	0.28
<b>Agomelatine</b>	N06AX22	2	672	0.3	76	3810	1.99	57	1596	3.57	28862 27	94547 5	0.17	0.13
<b>Tacrolimus</b>	D11AH01	2	458	0.44	11	562	1.96	10	252	3.97	28862 27	94547 5	0.03	0.02
<b>Posaconazole</b>	J02AC04	1	628	0.16	90	4768	1.89	38	964	3.94	28862 27	94547 5	0.1	0.17
<b>Rifampicin</b>	J04AB02	6	857	0.7	131	7229	1.81	102	4308	2.37	28862 27	94547 5	0.46	0.25
<b>Valproic acid</b>	N03AG01	2	1029	0.19	606	33631	1.8	458	10000	4.58	28862 27	94547 5	1.06	1.17

<b>Ibuprofen</b>	M01AE01	2	1437	0.14	9982	56922 3	1.75	7368	36530 2	2.02	28862 27	94547 5	38.64	19.72
<b>Clomipramine</b>	N06AA04	3	596	0.5	48	2852	1.68	21	824	2.55	28862 27	94547 5	0.09	0.1
<b>Drospirenone and ethinylestradio l</b>	G03AA12	3	419	0.72	20	1220	1.64	7	412	1.7	28862 27	94547 5	0.04	0.04
<b>Desogestrel</b>	G03AC09	4	335	1.19	7	436	1.61	5	201	2.49	28862 27	94547 5	0.02	0.02
<b>Medroxyproge sterone</b>	G03DA02	4	488	0.82	17	1156	1.47	5	374	1.34	28862 27	94547 5	0.04	0.04
<b>Ertapenem</b>	J01DH03	1	697	0.14	41	3009	1.36	32	2076	1.54	28862 27	94547 5	0.22	0.1
<b>Estriol</b>	G03CA04	3	645	0.47	39	3075	1.27	14	1211	1.16	28862 27	94547 5	0.13	0.11
<b>Oxcarbazepine</b>	N03AF02	4	868	0.46	131	10597	1.24	52	2986	1.74	28862 27	94547 5	0.32	0.37
<b>Methenamine</b>	J01XX05	1	620	0.16	31	2563	1.21	27	906	2.98	28862 27	94547 5	0.1	0.09
<b>Atazanavir</b>	J05AE08	3	507	0.59	22	1894	1.16	12	566	2.12	28862 27	94547 5	0.06	0.07
<b>Simvastatin</b>	C10AA01	8	1392	0.57	5048	44254 5	1.14	3887	14857 9	2.62	28862 27	94547 5	15.71	15.33
<b>Estradiol</b>	G03CA03	5	1058	0.47	344	31379	1.1	138	10795	1.28	28862 27	94547 5	1.14	1.09
<b>Diclofenac</b>	M01AB05	1	1245	0.08	1917	17792 8	1.08	1326	12025 6	1.1	28862 27	94547 5	12.72	6.16
<b>Meropenem</b>	J01DH02	1	1283	0.08	575	55688	1.03	439	36151	1.21	28862 27	94547 5	3.82	1.93
<b>Imipramine</b>	N06AA02	3	785	0.38	69	6844	1.01	45	2235	2.01	28862 27	94547 5	0.24	0.24
<b>Tacrolimus</b>	L04AD02	2	765	0.26	90	9708	0.93	68	1900	3.58	28862 27	94547 5	0.2	0.34
<b>Celecoxib</b>	M01AH01	1	996	0.1	661	72096	0.92	571	57153	1	28862 27	94547 5	6.04	2.5

<b>Naproxen</b>	M01AE02	2	811	0.25	165	18264	0.9	110	12381	0.89	28862 27	94547 5	1.31	0.63
<b>Everolimus</b>	L04AA18	2	459	0.44	15	1735	0.86	12	294	4.08	28862 27	94547 5	0.03	0.06
<b>Selegiline</b>	N04BD01	2	494	0.4	14	1698	0.82	6	544	1.1	28862 27	94547 5	0.06	0.06
<b>Venlafaxine</b>	N06AX16	3	1082	0.28	220	39070	0.56	149	12541	1.19	28862 27	94547 5	1.33	1.35
<b>Verapamil</b>	C08DA01	3	1036	0.29	221	41236	0.54	135	13786	0.98	28862 27	94547 5	1.46	1.43
<b>Tamoxifen</b>	L02BA01	2	620	0.32	21	4280	0.49	16	1974	0.81	28862 27	94547 5	0.21	0.15
<b>Phenobarbital</b>	N03AA02	9	945	0.95	107	24658	0.43	51	10612	0.48	28862 27	94547 5	1.12	0.85
<b>Allopurinol</b>	M04AA01	1	1181	0.08	315	76643	0.41	139	22843	0.61	28862 27	94547 5	2.42	2.66
<b>Quetiapine</b>	N05AH04	1	1134	0.09	297	74846	0.4	234	24677	0.95	28862 27	94547 5	2.61	2.59
<b>Nortriptyline</b>	N06AA10	2	1045	0.19	87	21962	0.4	60	7232	0.83	28862 27	94547 5	0.76	0.76
<b>Ticagrelor</b>	B01AC24	2	984	0.2	188	49328	0.38	155	30626	0.51	28862 27	94547 5	3.24	1.71
<b>Mianserin</b>	N06AX03	1	930	0.11	59	16501	0.36	21	6006	0.35	28862 27	94547 5	0.64	0.57
<b>Probenecid</b>	M04AB01	2	551	0.36	5	1435	0.35	5	469	1.07	28862 27	94547 5	0.05	0.05
<b>Midazolam</b>	N05CD08	2	1137	0.18	145	42109	0.34	108	33001	0.33	28862 27	94547 5	3.49	1.46
<b>Metoprolol</b>	C07AB02	1	1392	0.07	1191	37978 5	0.31	399	12723 7	0.31	28862 27	94547 5	13.46	13.16
<b>Apixaban</b>	B01AF02	1	811	0.12	49	16377	0.3	24	8230	0.29	28862 27	94547 5	0.87	0.57
<b>Nifedipine</b>	C08CA05	2	920	0.22	36	12454	0.29	30	4457	0.67	28862 27	94547 5	0.47	0.43



<b>Ciprofloxacin</b>	J01MA02	2	1384	0.14	393	13525 6	0.29	248	86572	0.29	28862 27	94547 5	9.16	4.69
<b>Letrozole</b>	L02BG04	1	761	0.13	25	9502	0.26	14	4067	0.34	28862 27	94547 5	0.43	0.33
<b>Sulfamethizole</b>	J01EB02	1	943	0.11	31	11944	0.26	27	10010	0.27	28862 27	94547 5	1.06	0.41
<b>Dabigatran etexilate</b>	B01AE07	2	899	0.22	81	32015	0.25	43	14549	0.3	28862 27	94547 5	1.54	1.11
<b>Atorvastatin</b>	C10AA05	1	1142	0.09	231	94086	0.25	64	36004	0.18	28862 27	94547 5	3.81	3.26
<b>Rosuvastatin</b>	C10AA07	1	967	0.1	54	23416	0.23	10	7811	0.13	28862 27	94547 5	0.83	0.81
<b>Zuclopenthixol</b>	N05AF05	1	823	0.12	25	14838	0.17	14	4039	0.35	28862 27	94547 5	0.43	0.51
<b>Cabergoline</b>	G02CB03	1	506	0.2	10	5821	0.17	10	4909	0.2	28862 27	94547 5	0.52	0.2
<b>Triazolam</b>	N05CD05	3	1118	0.27	43	66578	0.06	33	48423	0.07	28862 27	94547 5	5.12	2.31
<b>Mirtazapine</b>	N06AX11	1	1203	0.08	28	76274	0.04	13	27409	0.05	28862 27	94547 5	2.9	2.64
<b>Rivaroxaban</b>	B01AF01	1	973	0.1	9	53062	0.02	5	34144	0.01	28862 27	94547 5	3.61	1.84
<b>Lansoprazole</b>	A02BC03	1	1243	0.08	15	11873 7	0.01	6	43814	0.01	28862 27	94547 5	4.63	4.11
<b>Pantoprazole</b>	A02BC02	2	1518	0.13	9	57044 0	0	5	22400 2	0	28862 27	94547 5	23.69	19.76

**Table S3. Overview of drugs involved in discouraged combinations**

Drugs used by less than 5 patients were omitted to avoid privacy issues.

Drug name	ATC	Recommendation level	Clinical significance	Documentation	pDDIs (N)
Domperidone	A03FA03	5	Minor	Documented	2
Domperidone	A03FA03	5	None	Documented	2
Domperidone	A03FA03	1	Major	Limited documented	1
Warfarin	B01AA03	5	Minor	Documented	3
Warfarin	B01AA03	5	Minor	Well documented	3
Warfarin	B01AA03	5	Moderate	Poorly documented	1
Warfarin	B01AA03	5	None	Documented	56
Warfarin	B01AA03	5	None	Limited documented	4
Warfarin	B01AA03	5	None	Well documented	4
Warfarin	B01AA03	5	Possible	Documented	4
Warfarin	B01AA03	5	Undetermined	Documented	4
Warfarin	B01AA03	5	Undetermined	Poorly documented	12
Warfarin	B01AA03	5	Undetermined	Well documented	2
Warfarin	B01AA03	4	Major	Well documented	5
Warfarin	B01AA03	4	Minor	Documented	1
Warfarin	B01AA03	4	Moderate	Documented	6
Warfarin	B01AA03	4	Moderate	Limited documented	4
Warfarin	B01AA03	4	Moderate	Poorly documented	5
Warfarin	B01AA03	4	Moderate	Well documented	17
Warfarin	B01AA03	4	Possible	Documented	11
Warfarin	B01AA03	4	Possible	Limited documented	3
Warfarin	B01AA03	4	Possible	Poorly documented	5
Warfarin	B01AA03	4	Possible	Well documented	1
Warfarin	B01AA03	4	Undetermined	Documented	2
Warfarin	B01AA03	4	Undetermined	Poorly documented	3
Warfarin	B01AA03	2	Major	Documented	4
Warfarin	B01AA03	2	Major	Limited documented	4

<b>Warfarin</b>	B01AA03	2	Major	Well documented	2
<b>Warfarin</b>	B01AA03	2	Moderate	Documented	13
<b>Warfarin</b>	B01AA03	2	Moderate	Limited documented	1
<b>Warfarin</b>	B01AA03	2	Moderate	Poorly documented	3
<b>Warfarin</b>	B01AA03	2	Moderate	Well documented	6
<b>Warfarin</b>	B01AA03	2	Possible	Documented	1
<b>Warfarin</b>	B01AA03	2	Possible	Poorly documented	6
<b>Warfarin</b>	B01AA03	1	Major	Documented	5
<b>Warfarin</b>	B01AA03	1	Major	Poorly documented	6
<b>Warfarin</b>	B01AA03	1	Major	Well documented	4
<b>Warfarin</b>	B01AA03	1	Possible	Documented	1
<b>Phenprocoumon</b>	B01AA04	5	None	Documented	12
<b>Phenprocoumon</b>	B01AA04	5	None	Limited documented	2
<b>Phenprocoumon</b>	B01AA04	5	None	Poorly documented	2
<b>Phenprocoumon</b>	B01AA04	5	None	Well documented	1
<b>Phenprocoumon</b>	B01AA04	5	Undetermined	Limited documented	2
<b>Phenprocoumon</b>	B01AA04	4	Moderate	Documented	4
<b>Phenprocoumon</b>	B01AA04	4	Moderate	Poorly documented	4
<b>Phenprocoumon</b>	B01AA04	4	Possible	Documented	7
<b>Phenprocoumon</b>	B01AA04	4	Possible	Limited documented	2
<b>Phenprocoumon</b>	B01AA04	4	Possible	Poorly documented	2
<b>Phenprocoumon</b>	B01AA04	4	Undetermined	Limited documented	1
<b>Phenprocoumon</b>	B01AA04	4	Undetermined	Poorly documented	1
<b>Phenprocoumon</b>	B01AA04	2	Moderate	Documented	1
<b>Phenprocoumon</b>	B01AA04	2	Moderate	Poorly documented	2
<b>Phenprocoumon</b>	B01AA04	2	Possible	Poorly documented	1
<b>Phenprocoumon</b>	B01AA04	2	Undetermined	Limited documented	1
<b>Phenprocoumon</b>	B01AA04	1	Major	Documented	1
<b>Phenprocoumon</b>	B01AA04	1	Major	Well documented	1
<b>Ketoconazole</b>	D01AC08	5	Minor	Documented	3
<b>Ketoconazole</b>	D01AC08	5	Minor	Limited documented	3

<b>Ketoconazole</b>	D01AC08	5	None	Documented	11
<b>Ketoconazole</b>	D01AC08	5	None	Limited documented	5
<b>Ketoconazole</b>	D01AC08	5	Possible	Well documented	1
<b>Ketoconazole</b>	D01AC08	5	Undetermined	Documented	1
<b>Ketoconazole</b>	D01AC08	4	Major	Documented	2
<b>Ketoconazole</b>	D01AC08	4	Moderate	Documented	5
<b>Ketoconazole</b>	D01AC08	4	Possible	Documented	11
<b>Ketoconazole</b>	D01AC08	4	Possible	Well documented	1
<b>Ketoconazole</b>	D01AC08	3	Major	Documented	1
<b>Ketoconazole</b>	D01AC08	3	Possible	Poorly documented	7
<b>Ketoconazole</b>	D01AC08	2	Major	Documented	3
<b>Ketoconazole</b>	D01AC08	2	Major	Well documented	3
<b>Ketoconazole</b>	D01AC08	2	Minor	Documented	1
<b>Ketoconazole</b>	D01AC08	2	Moderate	Documented	20
<b>Ketoconazole</b>	D01AC08	2	Moderate	Poorly documented	1
<b>Ketoconazole</b>	D01AC08	2	Moderate	Well documented	3
<b>Ketoconazole</b>	D01AC08	2	Possible	Documented	1
<b>Ketoconazole</b>	D01AC08	1	Major	Documented	3
<b>Ketoconazole</b>	D01AC08	1	Major	Limited documented	3
<b>Erythromycin</b>	J01FA01	5	Minor	Documented	3
<b>Erythromycin</b>	J01FA01	5	Moderate	Poorly documented	1
<b>Erythromycin</b>	J01FA01	5	None	Documented	7
<b>Erythromycin</b>	J01FA01	5	None	Limited documented	1
<b>Erythromycin</b>	J01FA01	4	Major	Documented	2
<b>Erythromycin</b>	J01FA01	4	Major	Poorly documented	2
<b>Erythromycin</b>	J01FA01	4	Major	Well documented	1
<b>Erythromycin</b>	J01FA01	4	Moderate	Documented	2
<b>Erythromycin</b>	J01FA01	4	Possible	Documented	3
<b>Erythromycin</b>	J01FA01	4	Possible	Limited documented	2
<b>Erythromycin</b>	J01FA01	4	Possible	Well documented	1
<b>Erythromycin</b>	J01FA01	4	Undetermined	Documented	6
<b>Erythromycin</b>	J01FA01	4	Undetermined	Limited documented	1
<b>Erythromycin</b>	J01FA01	4	Undetermined	Poorly documented	1

<b>Erythromycin</b>	J01FA01	2	Major	Documented	1
<b>Erythromycin</b>	J01FA01	2	Major	Limited documented	1
<b>Erythromycin</b>	J01FA01	2	Moderate	Documented	6
<b>Erythromycin</b>	J01FA01	2	Moderate	Well documented	1
<b>Erythromycin</b>	J01FA01	2	Possible	Well documented	1
<b>Erythromycin</b>	J01FA01	2	Undetermined	Limited documented	1
<b>Erythromycin</b>	J01FA01	1	Major	Documented	2
<b>Erythromycin</b>	J01FA01	1	Major	Limited documented	3
<b>Erythromycin</b>	J01FA01	1	Major	Well documented	2
<b>Erythromycin</b>	J01FA01	1	Possible	Documented	1
<b>Clarithromycin</b>	J01FA09	5	Minor	Documented	4
<b>Clarithromycin</b>	J01FA09	5	Minor	Limited documented	1
<b>Clarithromycin</b>	J01FA09	5	Moderate	Poorly documented	1
<b>Clarithromycin</b>	J01FA09	5	None	Documented	4
<b>Clarithromycin</b>	J01FA09	5	None	Limited documented	1
<b>Clarithromycin</b>	J01FA09	5	Possible	Documented	1
<b>Clarithromycin</b>	J01FA09	5	Possible	Limited documented	1
<b>Clarithromycin</b>	J01FA09	5	Possible	Poorly documented	2
<b>Clarithromycin</b>	J01FA09	5	Undetermined	Limited documented	1
<b>Clarithromycin</b>	J01FA09	5	Undetermined	Poorly documented	2
<b>Clarithromycin</b>	J01FA09	4	Major	Documented	3
<b>Clarithromycin</b>	J01FA09	4	Major	Poorly documented	14
<b>Clarithromycin</b>	J01FA09	4	Moderate	Documented	1
<b>Clarithromycin</b>	J01FA09	4	Moderate	Limited documented	2
<b>Clarithromycin</b>	J01FA09	4	Moderate	Poorly documented	1
<b>Clarithromycin</b>	J01FA09	4	Moderate	Well documented	2
<b>Clarithromycin</b>	J01FA09	4	None	Documented	1
<b>Clarithromycin</b>	J01FA09	4	Possible	Documented	7
<b>Clarithromycin</b>	J01FA09	4	Possible	Limited documented	2
<b>Clarithromycin</b>	J01FA09	4	Possible	Well documented	2
<b>Clarithromycin</b>	J01FA09	4	Undetermined	Poorly documented	2

<b>Clarithromycin</b>	J01FA09	3	Moderate	Poorly documented	2
<b>Clarithromycin</b>	J01FA09	2	Major	Well documented	1
<b>Clarithromycin</b>	J01FA09	2	Moderate	Documented	6
<b>Clarithromycin</b>	J01FA09	2	Moderate	Limited documented	1
<b>Clarithromycin</b>	J01FA09	2	Moderate	Well documented	1
<b>Clarithromycin</b>	J01FA09	2	Possible	Documented	2
<b>Clarithromycin</b>	J01FA09	2	Possible	Limited documented	2
<b>Clarithromycin</b>	J01FA09	2	Possible	Well documented	1
<b>Clarithromycin</b>	J01FA09	2	Undetermined	Documented	2
<b>Clarithromycin</b>	J01FA09	1	Major	Documented	8
<b>Clarithromycin</b>	J01FA09	1	Major	Poorly documented	4
<b>Clarithromycin</b>	J01FA09	1	Moderate	Documented	2
<b>Ketoconazole</b>	J02AB02	5	None	Documented	6
<b>Ketoconazole</b>	J02AB02	5	Undetermined	Documented	1
<b>Ketoconazole</b>	J02AB02	4	Moderate	Documented	2
<b>Ketoconazole</b>	J02AB02	4	Possible	Documented	1
<b>Ketoconazole</b>	J02AB02	3	Possible	Poorly documented	4
<b>Ketoconazole</b>	J02AB02	2	Major	Documented	1
<b>Ketoconazole</b>	J02AB02	2	Major	Well documented	2
<b>Ketoconazole</b>	J02AB02	2	Moderate	Documented	5
<b>Ketoconazole</b>	J02AB02	2	Moderate	Poorly documented	1
<b>Ketoconazole</b>	J02AB02	2	Moderate	Well documented	3
<b>Ketoconazole</b>	J02AB02	1	Major	Documented	1
<b>Ketoconazole</b>	J02AB02	1	Major	Limited documented	1
<b>Rifabutin</b>	J04AB04	5	Minor	Documented	1
<b>Rifabutin</b>	J04AB04	5	Minor	Poorly documented	1
<b>Rifabutin</b>	J04AB04	5	None	Documented	3
<b>Rifabutin</b>	J04AB04	4	Moderate	Documented	1
<b>Rifabutin</b>	J04AB04	4	Moderate	Well documented	1
<b>Rifabutin</b>	J04AB04	4	Possible	Documented	1
<b>Rifabutin</b>	J04AB04	2	Major	Documented	1
<b>Rifabutin</b>	J04AB04	2	Moderate	Documented	3
<b>Rifabutin</b>	J04AB04	2	Possible	Well documented	1
<b>Rifabutin</b>	J04AB04	1	Major	Documented	1

<b>Rifabutin</b>	J04AB04	1	Moderate	Documented	1
<b>Imatinib</b>	L01XE01	5	None	Documented	9
<b>Imatinib</b>	L01XE01	5	Possible	Poorly documented	1
<b>Imatinib</b>	L01XE01	5	Undetermined	Poorly documented	1
<b>Imatinib</b>	L01XE01	4	Minor	Documented	1
<b>Imatinib</b>	L01XE01	4	Moderate	Documented	1
<b>Imatinib</b>	L01XE01	4	Moderate	Limited documented	1
<b>Imatinib</b>	L01XE01	4	Moderate	Poorly documented	2
<b>Imatinib</b>	L01XE01	4	Possible	Limited documented	1
<b>Imatinib</b>	L01XE01	4	Possible	Poorly documented	1
<b>Imatinib</b>	L01XE01	2	Moderate	Documented	1
<b>Imatinib</b>	L01XE01	2	Possible	Documented	2
<b>Imatinib</b>	L01XE01	1	Major	Documented	1
<b>Sirolimus</b>	L04AA10	5	None	Documented	2
<b>Sirolimus</b>	L04AA10	4	Major	Poorly documented	1
<b>Sirolimus</b>	L04AA10	4	Moderate	Limited documented	1
<b>Sirolimus</b>	L04AA10	4	Moderate	Poorly documented	1
<b>Sirolimus</b>	L04AA10	2	Major	Documented	1
<b>Sirolimus</b>	L04AA10	2	Major	Limited documented	3
<b>Sirolimus</b>	L04AA10	2	Moderate	Limited documented	1
<b>Sirolimus</b>	L04AA10	2	Possible	Well documented	1
<b>Sirolimus</b>	L04AA10	2	Undetermined	Documented	1
<b>Sirolimus</b>	L04AA10	1	Major	Documented	1
<b>Sirolimus</b>	L04AA10	1	Major	Limited documented	1
<b>Sirolimus</b>	L04AA10	1	Major	Poorly documented	1
<b>Etoricoxib</b>	M01AH05	5	Minor	Documented	2
<b>Etoricoxib</b>	M01AH05	5	None	Documented	3
<b>Etoricoxib</b>	M01AH05	4	Undetermined	Poorly documented	1
<b>Etoricoxib</b>	M01AH05	2	Possible	Documented	1
<b>Etoricoxib</b>	M01AH05	1	Major	Documented	1
<b>Tizanidine</b>	M03BX02	4	Moderate	Limited documented	3
<b>Tizanidine</b>	M03BX02	4	Possible	Documented	1
<b>Tizanidine</b>	M03BX02	4	Possible	Poorly documented	2

<b>Tizanidine</b>	M03BX02	1	Major	Documented	3
<b>Paroxetine</b>	N06AB05	5	None	Documented	10
<b>Paroxetine</b>	N06AB05	5	Possible	Poorly documented	2
<b>Paroxetine</b>	N06AB05	4	Major	Poorly documented	2
<b>Paroxetine</b>	N06AB05	4	Major	Well documented	1
<b>Paroxetine</b>	N06AB05	4	Minor	Documented	2
<b>Paroxetine</b>	N06AB05	4	Moderate	Documented	3
<b>Paroxetine</b>	N06AB05	4	Moderate	Limited documented	1
<b>Paroxetine</b>	N06AB05	4	Moderate	Poorly documented	11
<b>Paroxetine</b>	N06AB05	4	Moderate	Well documented	2
<b>Paroxetine</b>	N06AB05	4	Possible	Documented	7
<b>Paroxetine</b>	N06AB05	4	Possible	Limited documented	2
<b>Paroxetine</b>	N06AB05	4	Possible	Poorly documented	1
<b>Paroxetine</b>	N06AB05	4	Undetermined	Documented	1
<b>Paroxetine</b>	N06AB05	4	Undetermined	Poorly documented	1
<b>Paroxetine</b>	N06AB05	2	Moderate	Documented	1
<b>Paroxetine</b>	N06AB05	2	None	Documented	1
<b>Paroxetine</b>	N06AB05	1	Major	Documented	3
<b>Paroxetine</b>	N06AB05	1	Moderate	Well documented	1
<b>Isocarboxazid</b>	N06AF01	4	Major	Limited documented	2
<b>Isocarboxazid</b>	N06AF01	4	Major	Poorly documented	1
<b>Isocarboxazid</b>	N06AF01	4	Moderate	Limited documented	3
<b>Isocarboxazid</b>	N06AF01	4	Moderate	Poorly documented	1
<b>Isocarboxazid</b>	N06AF01	4	Possible	Poorly documented	1
<b>Isocarboxazid</b>	N06AF01	1	Major	Poorly documented	3
<b>Isocarboxazid</b>	N06AF01	1	Undetermined	Poorly documented	1



**Table S4. List of discouraged drug pairs**

Discouraged drug pairs dispensed in at least 5 admissions ( $\geq 5$  patients) prescribed during patient hospitalisation.

<b>Drug 1</b>	<b>Drug 2</b>	<b>Admissions (N)</b>
Warfarin (B01AA03)	Ibuprofen (M01AE01)	5,960
Simvastatin (C10AA01)	Clarithromycin (J01FA09)	2,354
Domperidone (A03FA03)	Fluconazole (J02AC01)	1,664
Erythromycin (J01FA01)	Fluconazole (J02AC01)	917
Warfarin (B01AA03)	Diclofenac (M01AB05)	815
Simvastatin (C10AA01)	Erythromycin (J01FA01)	525
Meropenem (J01DH02)	Valproic acid (N03AG01)	444
Warfarin (B01AA03)	Celecoxib (M01AH01)	327
Ciprofloxacin (J01MA02)	Tizanidine (M03BX02)	204
Clarithromycin (J01FA09)	Quetiapine (N05AH04)	194
Metoprolol (C07AB02)	Paroxetine (N06AB05)	175
Simvastatin (C10AA01)	Ketoconazole (D01AC08)	173
Clonidine (N02CX02)	Amitriptyline (N06AA09)	163
Warfarin (B01AA03)	Etodolac (M01AB08)	119
Ticagrelor (B01AC24)	Clarithromycin (J01FA09)	93
Terbinafine (D01AE15)	Amitriptyline (N06AA09)	84
Fluoxetine (N06AB03)	Venlafaxine (N06AX16)	81
Phenprocoumon (B01AA04)	Ibuprofen (M01AE01)	76
Carbamazepine (N03AF01)	Midazolam (N05CD08)	74
Pravastatin (C10AA03)	Ciclosporin (L04AD01)	72
Verapamil (C08DA01)	Colchicine (M04AC01)	70
Warfarin (B01AA03)	Naproxen (M01AE02)	64
Azathioprine (L04AX01)	Allopurinol (M04AA01)	58
Ciprofloxacin (J01MA02)	Agomelatine (N06AX22)	45
Terbinafine (D01AE15)	Nortriptyline (N06AA10)	43
Simvastatin (C10AA01)	Posaconazole (J02AC04)	42
Atorvastatin (C10AA05)	Ciclosporin (L04AD01)	39
Erythromycin (J01FA01)	Tacrolimus (L04AD02)	38
Verapamil (C08DA01)	Rifampicin (J04AB02)	29
Clarithromycin (J01FA09)	Tacrolimus (L04AD02)	27
Estradiol (G03CA03)	Carbamazepine (N03AF01)	26
Nifedipine (C08CA05)	Rifampicin (J04AB02)	24
Voriconazole (J02AC03)	Rifampicin (J04AB02)	22
Ketoconazole (D01AC08)	Clarithromycin (J01FA09)	21

Ertapenem (J01DH03)	Valproic acid (N03AG01)	20
Sulfamethizole (J01EB02)	Methenamine (J01XX05)	19
Ritonavir (J05AE03)	Triazolam (N05CD05)	19
Simvastatin (C10AA01)	Imatinib (L01XE01)	19
Simvastatin (C10AA01)	Itraconazole (J02AC02)	18
Voriconazole (J02AC03)	Sirolimus (L04AA10)	18
Dabigatran etexilate (B01AE07)	Dronedarone (C01BD07)	17
Estradiol (G03CA03)	Phenobarbital (N03AA02)	16
Clonidine (N02CX02)	Imipramine (N06AA02)	15
Apixaban (B01AF02)	Ketoconazole (D01AC08)	15
Isocarboxazid (N06AF01)	Mianserin (N06AX03)	14
Terbinafine (D01AE15)	Imipramine (N06AA02)	14
Estradiol (G03CA03)	Oxcarbazepine (N03AF02)	12
Warfarin (B01AA03)	Diclofenac, combinations (M01AB55)	12
Warfarin (B01AA03)	Piroxicam (M02AA07)	11
Warfarin (B01AA03)	Diclofenac (M02AA15)	11
Terbinafine (D01BA02)	Amitriptyline (N06AA09)	10
Warfarin (B01AA03)	Nabumetone (M01AX01)	10
Clarithromycin (J01FA09)	Everolimus (L04AA18)	9
Letrozole (L02BG04)	Zuclopenthixol (N05AF05)	8
Warfarin (B01AA03)	Diclofenac (S01BC03)	8
Terbinafine (D01BA02)	Nortriptyline (N06AA10)	7
Rifabutin (J04AB04)	Ritonavir (J05AE03)	7
Isocarboxazid (N06AF01)	Mirtazapine (N06AX11)	7
Clonidine (N02CX02)	Clomipramine (N06AA04)	7
Ticagrelor (B01AC24)	Ciclosporin (L04AD01)	7
Rifampicin (J04AB02)	Atazanavir (J05AE08)	5
Cabergoline (G02CB03)	Clarithromycin (J01FA09)	5
Dabigatran etexilate (B01AE07)	Ketoconazole (D01AC08)	5
Tacrolimus (D11AH01)	Clarithromycin (J01FA09)	5
Lansoprazole (A02BC03)	Atazanavir (J05AE08)	5

**Table S5. Effect-size estimates of exposure to discouraged drug pairs on post-discharge mortality, readmission and length-of-stay**

Provides numerical estimate illustrated in Figure 3: estimate (95 confidence interval). Mortality and readmission estimates are hazard ratios. Values below 1 are shown with 2 significant digits, otherwise with 1 significant digit.

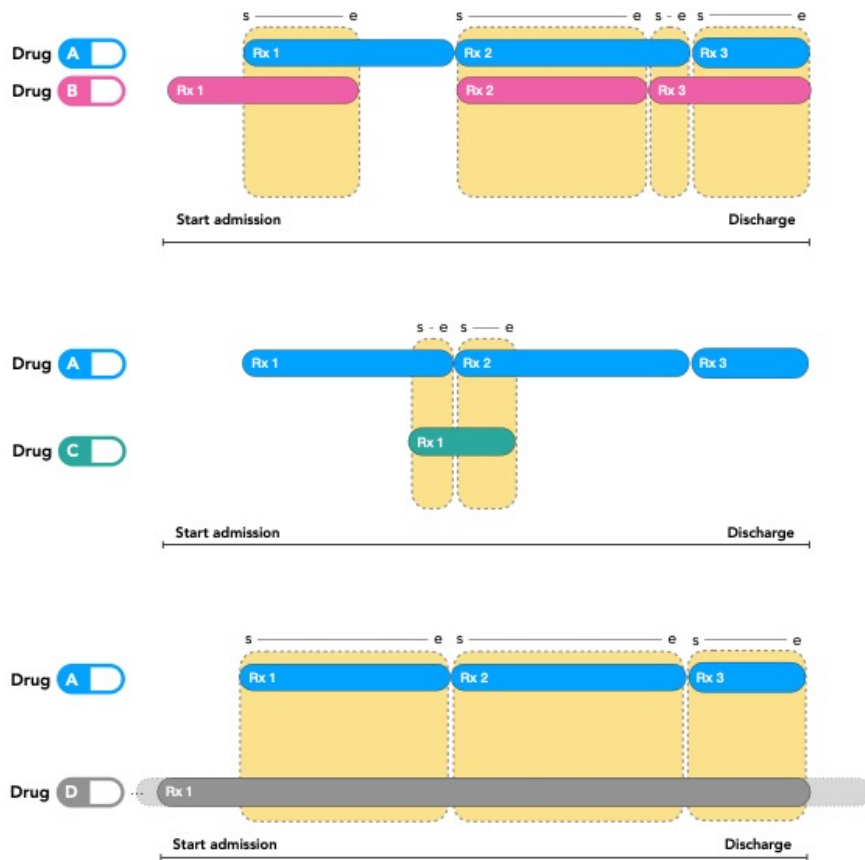
Clinical significance	Drug pair	Mortality	Readmission	LOS
<b>Moderate</b>	Estradiol +	-	0.74 (0.16; 3.4)	0.21 (-0.088; 0.51)
	Phenobarbital			
<b>Moderate</b>	Carbamazepine +	0.45 (0.1; 2)	0.97 (0.47; 2)	0.2 (0.0049; 0.39)
	Estradiol			
<b>Moderate</b>	Estradiol + Oxcarbazepine	0.78 (0.21; 2.9)	2.2 (0.81; 6)	-0.036 (-0.23; 0.15)
	Naproxen +			
<b>Major</b>	Warfarin	1.3 (0.61; 2.7)	0.92 (0.56; 1.5)	-0.14 (-0.24; -0.032)
	Apixaban +			
<b>Major</b>	Ketoconazole	2.5 (0.81; 7.7)	1.6 (0.82; 3.2)	-0.022 (-0.18; 0.14)
	Erythromycin +			
<b>Major</b>	Fluconazole	0.99 (0.73; 1.3)	0.72 (0.58; 0.89)	-0.089 (-0.12; -0.056)
	Imatinib +			
<b>Major</b>	Simvastatin	1.1 (0.4; 3.2)	1.5 (0.66; 3.6)	-0.12 (-0.38; 0.13)
	Atorvastatin +			
<b>Major</b>	Ciclosporin	0.73 (0.24; 2.3)	1.7 (0.78; 3.6)	0.77 (0.64; 0.9)
	Carbamazepine +			
<b>Major</b>	Midazolam	1.5 (0.77; 2.9)	0.7 (0.44; 1.1)	-0.004 (-0.083; 0.075)
	Celecoxib +			
<b>Possible</b>	Warfarin	0.78 (0.45; 1.4)	1.2 (0.85; 1.7)	0.036 (-0.04; 0.11)
	Isocarboxazid +			
<b>Un-determined</b>	Mianserin	-	0.78 (0.15; 3.9)	0.26 (-0.18; 0.7)
	Diclofenac (topical) +			
<b>Major</b>	Warfarin	0.96 (0.26; 3.5)	1.7 (0.66; 4.6)	0.8 (0.64; 0.97)
	Posaconazole +			
<b>Major</b>	Simvastatin	7.9 (0.71; 88)	1.3 (0.27; 6.7)	1.1 (0.91; 1.3)
	Ciclosporin +			
<b>Major</b>	Ticagrelor	-	4.2 (0.58; 29.9)	0.31 (-0.053; 0.66)
	Clarithromycin +			
<b>Major</b>	Tacrolimus (immunosupp.)	2.3 (0.64; 8.4)	3.4 (1.1; 10.4)	0.12 (-0.098; 0.34)

<b>Major</b>	Paroxetine + Tamoxifen	1.4 (0.27; 7.3)	1.9 (0.33; 10.4)	1.1 (0.78; 1.4)
<b>Moderate</b>	Itraconazole + Simvastatin	2.4 (0.75; 7.9)	2.5 (0.92; 6.6)	1.1 (0.93; 1.2)
<b>Major</b>	Diclofenac, combinations + Warfarin	1.5 (0.39; 5.9)	1.6 (0.61; 4.3)	-0.1 (-0.38; 0.17)
<b>Major</b>	Clonidine + Imipramine	0.87 (0.095; 7.9)	0.83 (0.31; 2.3)	0.38 (0.21; 0.54)
<b>Moderate</b>	Meropenem + Valproic acid	1.5 (1.1; 1.9)	0.92 (0.76; 1.1)	0.22 (0.19; 0.26)
<b>Major</b>	Nifedipine + Rifampicin	1.1 (0.13; 10.2)	1.2 (0.45; 3)	0.1 (-0.11; 0.31)
<b>Moderate</b>	Colchicine + Verapamil	0.61 (0.29; 1.3)	1 (0.63; 1.7)	0.13 (0.032; 0.23)
<b>Major</b>	Ketoconazole + Simvastatin	1 (0.68; 1.6)	1.3 (0.91; 1.8)	1.1 (1.1; 1.1)
<b>Moderate</b>	Fluoxetine + Venlafaxine	-	1.3 (0.4; 4.2)	-0.38 (-0.7; - 0.063)
<b>Major</b>	Etoricoxib + Warfarin	2.8 (0.17; 47.1)	0.82 (0.17; 3.8)	-0.77 (-1.2; -0.36)
<b>Major</b>	Amitriptyline + Terbinafine (systemic)	2.1 (0.53; 8)	3.1 (1.1; 8.8)	-0.39 (-0.63; - 0.15)
<b>Major</b>	Imipramine + Terbinafine	3.8 (1.2; 12)	1 (0.42; 2.4)	0.46 (0.29; 0.62)
<b>Major</b>	Clarithromycin + Everolimus	0.97 (0.1; 9)	12.3 (1.1; 138.7)	-1.2 (-1.9; -0.44)
<b>Major</b>	Ibuprofen + Phenprocoumon	0.81 (0.48; 1.4)	1.2 (0.86; 1.7)	0.2 (0.12; 0.27)
<b>Major</b>	Clarithromycin + Quetiapine	1.7 (1.1; 2.7)	0.94 (0.66; 1.3)	1.6 (1.5; 1.6)
<b>Major</b>	Ritonavir + Triazolam	3.6 (0.49; 26.1)	2.6 (0.84; 8.1)	-0.26 (-0.53; 0.0016)
<b>Major</b>	Rifampicin + Voriconazole	0.65 (0.077; 5.4)	1.3 (0.39; 4.2)	0.067 (-0.13; 0.26)
<b>Major</b>	Piroxicam + Warfarin	3.4 (1; 11.4)	1.4 (0.53; 3.9)	0.034 (-0.19; 0.25)

<b>Major</b>	Diclofenac (systemic) + Warfarin	0.83 (0.69; 1)	1.1 (0.96; 1.2)	0.25 (0.23; 0.28)
<b>Major</b>	Ertapenem + Valproic acid	1.3 (0.54; 3.1)	2.6 (1.1; 5.8)	0.24 (0.11; 0.38)
<b>Major</b>	Dabigatran etexilate + Ketoconazole	-	0.68 (0.14; 3.2)	0.06 (-0.26; 0.38)
<b>Major</b>	Diclofenac (ophthalmologica) + Warfarin	0.83 (0.23; 3)	1.7 (0.72; 4)	0.45 (0.27; 0.62)
<b>Major</b>	Clarithromycin + Ticagrelor	0.98 (0.51; 1.9)	1.7 (1.1; 2.5)	-0.25 (-0.34; -0.16)
<b>Major</b>	Clarithromycin + Ketoconazole	1.2 (0.24; 5.8)	0.56 (0.19; 1.7)	0.096 (-0.12; 0.31)
<b>Moderate</b>	Estriol + Phenobarbital	-	0.45 (0.052; 4)	-0.13 (-0.63; 0.38)
<b>Major</b>	Sirolimus + Voriconazole	0.51 (0.056; 4.6)	2.7 (0.45; 16.5)	-0.21 (-0.74; 0.32)
<b>Major</b>	Ciprofloxacin + Tizanidine	1.4 (0.92; 2.1)	1.4 (0.99; 1.9)	0.36 (0.29; 0.42)
<b>Major</b>	Ciclosporin + Pravastatin	0.22 (0.027; 1.7)	0.86 (0.22; 3.3)	-0.42 (-0.77; -0.073)
<b>Major</b>	Allopurinol + Azathioprine	0.93 (0.39; 2.2)	0.87 (0.49; 1.6)	0.092 (-0.036; 0.22)
<b>Major</b>	Rifabutin + Ritonavir	-	-	0.51 (0.091; 0.93)
<b>Major</b>	Nabumetone + Warfarin	0.99 (0.2; 4.8)	0.67 (0.18; 2.4)	-0.69 (-0.98; -0.39)
<b>Major</b>	Domperidone + Fluconazole	2.5 (2.1; 3.1)	1 (0.89; 1.2)	0.29 (0.27; 0.32)
<b>Major</b>	Methenamine + Sulfamethizole	1.7 (0.64; 4.6)	1.4 (0.67; 2.8)	0.81 (0.7; 0.92)
<b>Major</b>	Erythromycin + Tacrolimus	0.55 (0.066; 4.5)	0.81 (0.22; 3)	0.42 (0.17; 0.67)
<b>Major</b>	Rifampicin + Verapamil	0.7 (0.28; 1.8)	1.4 (0.67; 2.7)	0.36 (0.24; 0.47)
<b>Moderate</b>	Metoprolol + Paroxetine	1.1 (0.72; 1.7)	0.92 (0.67; 1.3)	0.088 (0.026; 0.15)

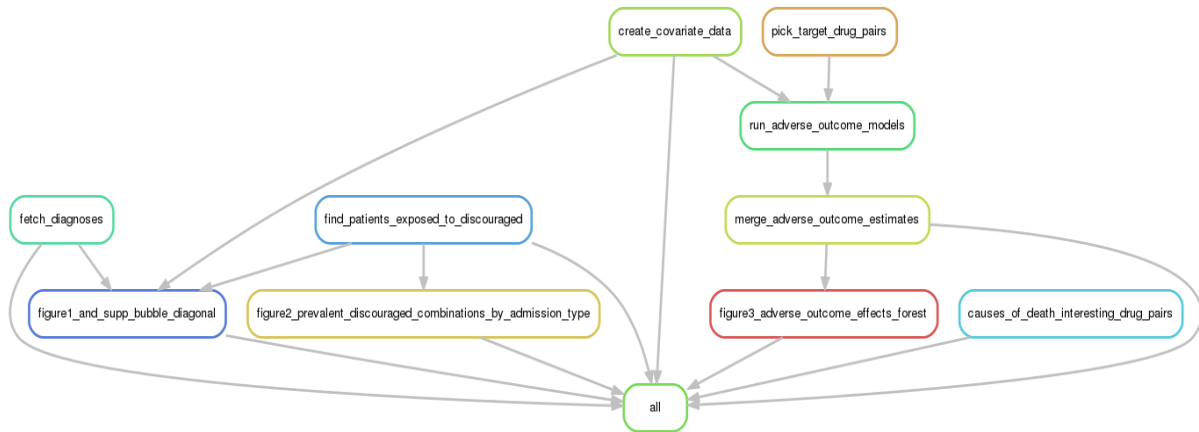
<b>Major</b>	Amitriptyline + Clonidine	1.1 (0.62; 1.8)	1.1 (0.77; 1.6)	-0.16 (-0.23; - 0.085)
<b>Major</b>	Ibuprofen + Warfarin	0.9 (0.83; 0.98)	1.1 (1; 1.2)	0.006 (-0.0062; 0.018)
<b>Major</b>	Amitriptyline + Terbinafine (topical)	1.1 (0.66; 1.9)	1 (0.73; 1.5)	0.54 (0.48; 0.6)
<b>Major</b>	Clarithromycin + Simvastatin	1.1 (0.95; 1.2)	1 (0.92; 1.1)	0.082 (0.063; 0.1)
<b>Major</b>	Agomelatine + Ciprofloxacin	2.6 (1.3; 5.5)	1.1 (0.62; 1.9)	0.82 (0.73; 0.9)
<b>Major</b>	Nortriptyline + Terbinafine (systemic)	4.3 (0.86; 21.8)	1.7 (0.43; 6.6)	-0.29 (-0.61; 0.032)
<b>Major</b>	Nortriptyline + Terbinafine (topical)	1.1 (0.46; 2.6)	1.1 (0.65; 2)	0.67 (0.58; 0.77)
<b>Major</b>	Etodolac + Warfarin	0.76 (0.43; 1.3)	1.1 (0.78; 1.6)	-0.15 (-0.23; - 0.07)
<b>Possible</b>	Erythromycin + Simvastatin	1.1 (0.83; 1.3)	1.1 (0.93; 1.4)	0.067 (0.033; 0.1)
<b>Major</b>	Clarithromycin + Tacrolimus (topical)	-	0.51 (0.062; 4.2)	-0.087 (-0.54; 0.37)
<b>Major</b>	Clomipramine + Clonidine	0.55 (0.065; 4.6)	1.4 (0.43; 4.8)	-0.22 (-0.47; 0.029)

**Figure S1. Concomitant drug exposure**



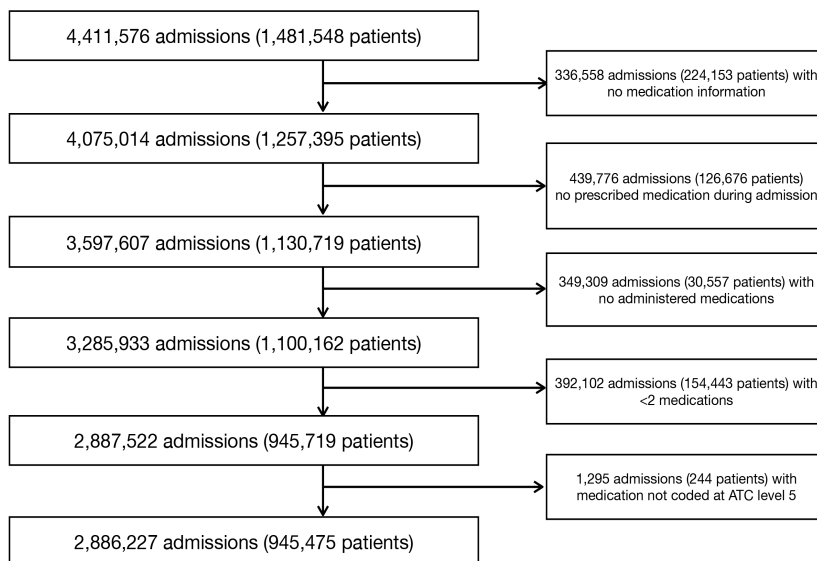
Concomitant drug exposures were defined as two temporally overlapping active drug prescriptions, during admission. The start (s) and the end (e) of the overlaps were defined at the first and last overlapping timestamps for each pair of prescriptions, respectively. Three examples are represented in the top, middle and bottom where yellow boxes represent overlaps. Only active drug prescriptions that were dispensed/administered at the hospital were considered. Adapted from supplementary figure 10 in Leal et al [16].

**Figure S2. Pipeline workflow**



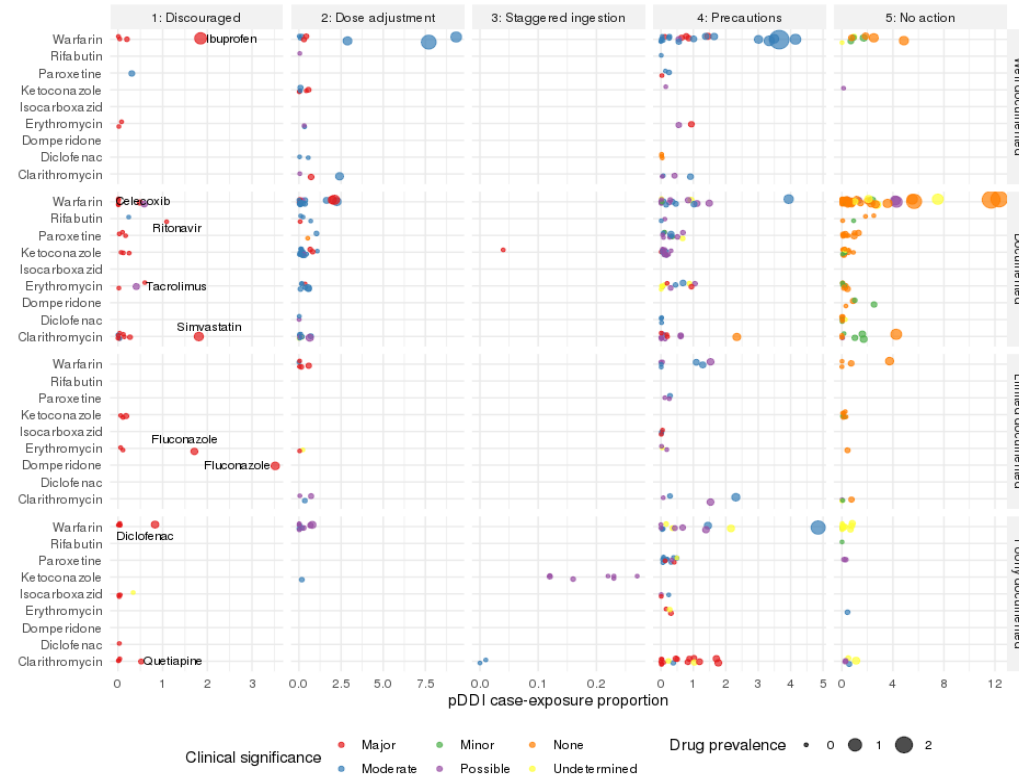
Snakemake pipeline depicting the workflow used for the adverse outcomes analytic part of the study. Schematic overview of the analytic pipeline. Each box represents a distinct step, and arrows represent dependencies between tasks. Preprocessing not depicted.

**Figure S3. Attrition diagram**



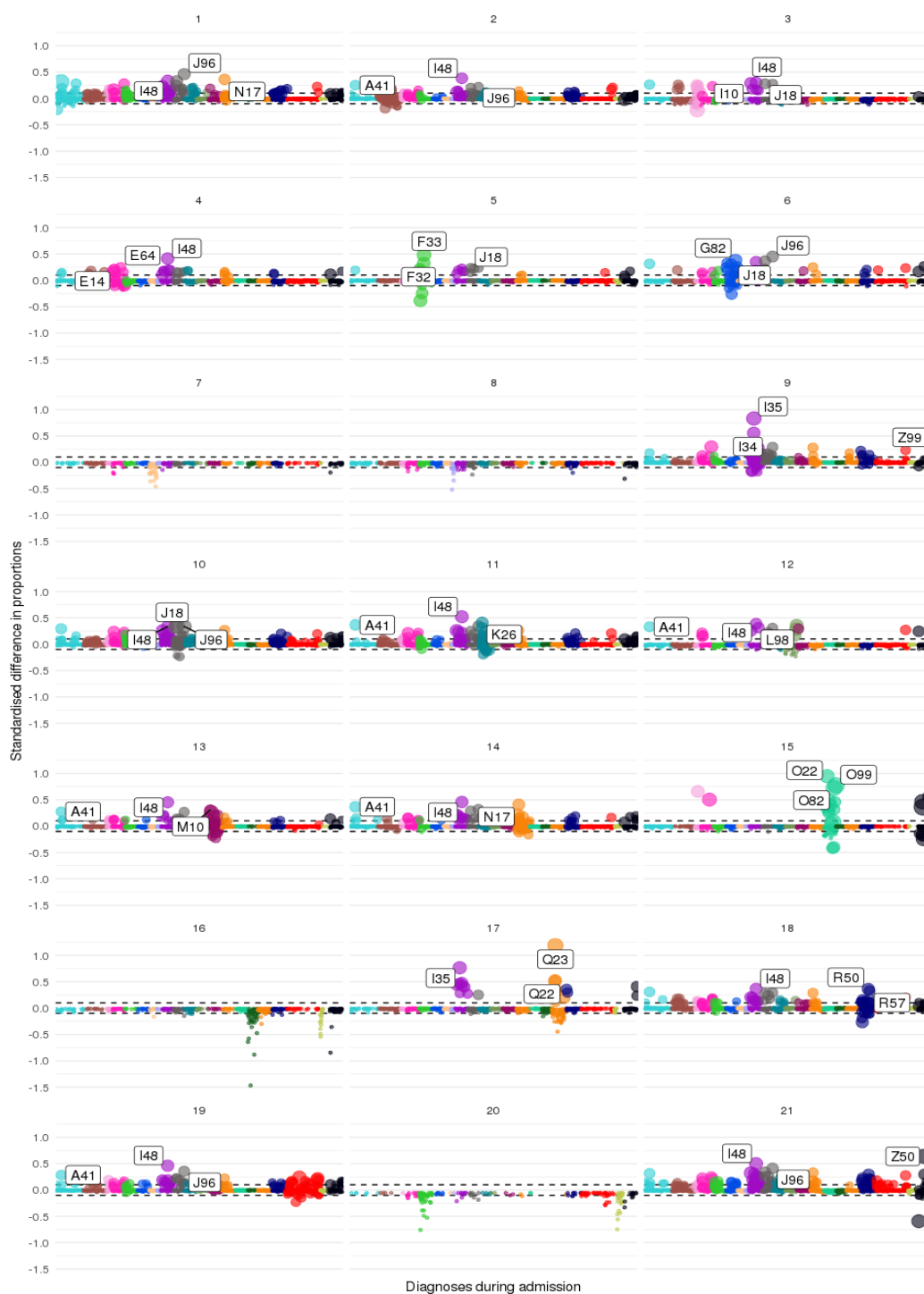


**Figure S4. Drugs prevalently involved in discouraged drug pairs**



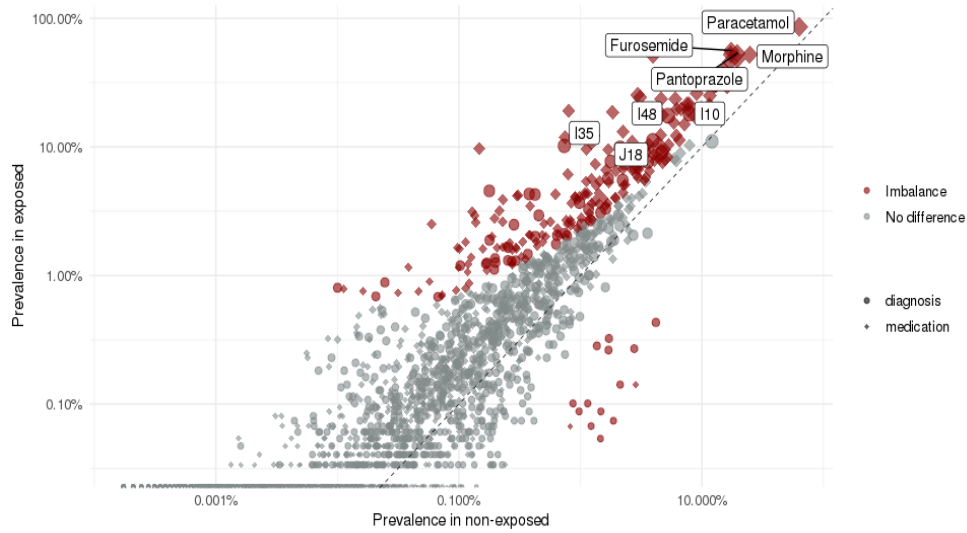
Drugs prevalently involved in discouraged drug pairs by management recommendation (columns) and clinical significance (rows), defined as drugs involved in discouraged drug pairs occurring in at least 10 of admissions. Points represent pDDIs, size the drug prevalence, and colour the clinical significance.

**Figure S5. Standardised differences in proportions of diagnoses in admissions with and without discouraged drug pairs by patient type**



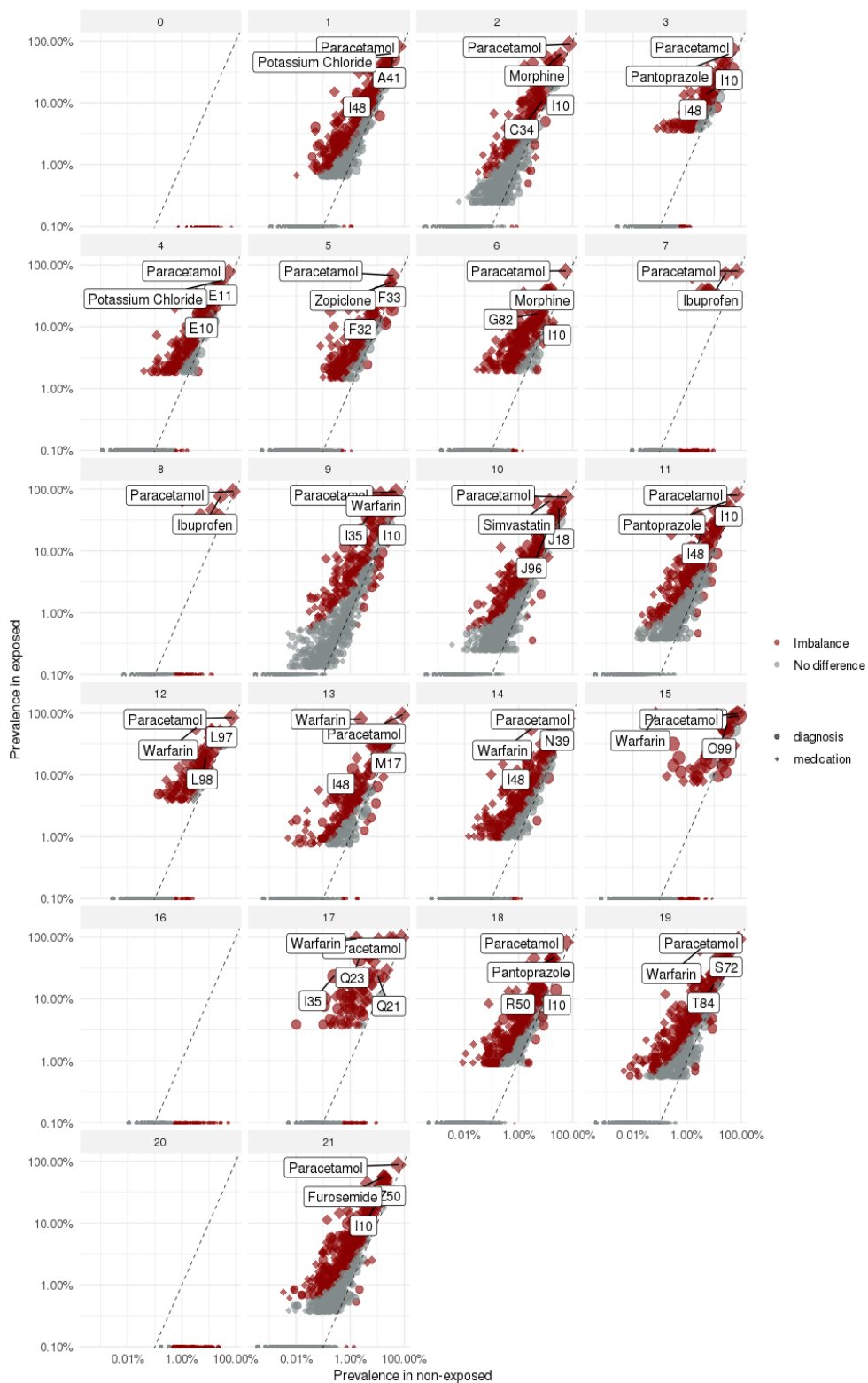
Standardised differences in proportions (i.e. discouraged drug pairs initiated versus not) of diagnoses and during admissions. The colour represents ICD-10 chapter, and the size is the prevalence in patients exposed to discouraged drug pairs. The top three diagnoses and drugs are labelled.

**Figure S6. Phenotyping of diagnoses and medications**



Detailed diagnoses and medication phenotyping of patients exposed to discouraged drug pairs vs. those not exposed. The plot compares the diagnoses and medications during hospitalisation. Each dot represents one of these covariates with the colour indicating the absolute value of the standardized difference in proportion (SPD). The top three medications and diagnoses with SPD > 0.1 (exposed; red) are highlighted.

**Figure S7. Phenotyping of diagnoses and medications by patient type**



Same as eFigure 5 but by patient type.

**Figure S8. Causes of death at ICD-10 chapter level among deceased exposed to selected drug pairs**

