Drug Safety

Timing Matters: A Machine Learning Method for the Prioritization of Drug-Drug Interactions through Signal Detection in the FDA Adverse Event Reporting System and Their Relationship with Time of Co-exposure

Vera Battini[1,2]*, Marianna Cocco[1], Maria Antonietta Barbieri[3], Greg Powell[4], Carla Carnovale[2], Emilio Clementi[2,5], Andrew Bate[6,7], and Maurizio Sessa[1]

[1] Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

[2] Pharmacovigilance & Clinical Research, International Centre for Pesticides and Health Risk Prevention, Department of Biomedical and Clinical Sciences (DIBIC), ASST Fatebenefratelli-Sacco University Hospital, Università degli Studi di Milano, Milan, Italy.

[3] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.

[4] Safety Innovation and Analytics, GSK, Durham, NC, USA.

[5] Scientific Institute, IRCCS E. Medea, Bosisio Parini, LC, Italy.

[6] GSK, London, UK.

[7] London School of Hygiene and Tropical Medicine, University of London, London, UK.

Corresponding author:

Vera Battini, MPharm, Cand. PhD

Department of Drug Design and Pharmacology,

University of Copenhagen,

Jagtvej 160, Copenhagen 2100, Capital Region, Denmark

vera.battini@unimi.it

Supplementary Table S1 Temporal plausibility of disproportionality signals for DDIs considering time of co-exposure

AE	DDI	Type of interaction	Temporal Plausibility		Reference
			Flex point (days)	Acceptable	
Bradycardia	Digoxin ± Bisoprolol	PD	1	Y	[1]
Confusional state	Amitriptyline ± Duloxetine	Synergic Effect	1	Y	[2]
QT prolonged	Clomipramine ± Quetiapine	Synergic Effect	1	?	[3]
	Clomipramine ± Venlafaxine	Synergic Effect	1	?	[3]
Haemorrhage	Enoxaparin ± Ticagrelor	Synergic Effect	1	Y	[4–6]
	Ticagrelor ± Heparin	Synergic Effect	1	Y	[4,5]
	Enoxaparin ± Clopidogrel	Synergic Effect	1	Y	[6]
	Apixaban ± Ticagrelor	Synergic Effect	1	Y	[7]
	Apixaban ± Prasugrel	Synergic Effect	1	Y	[7]
	Fondaparinux ± Ticagrelor	Synergic Effect	1	Y	[8]
	Fondaparinux ± Clopidogrel	Synergic Effect	1	Y	[8]
	Alteplase ± Heparin	Synergic Effect	1	?	[9–11]
	Warfarin ± Clopidogrel	Synergic Effect	1	?	[12–14]
	Warfarin ± Rivaroxaban	Synergic Effect	1	Y	[15,16]
	Ibuprofen ± Clopidogrel	Synergic Effect	1	Y	[17]
Hyperkalaemia	Trimethoprim ± Lisinopril	Synergic Effect	1	?	[18,19]
	Enalapril ± Trimethoprim	Synergic Effect	3	?	[18,19]
Hyponatraemia	Duloxetine ± Escitalopram	Synergic Effect	1	Y	[20,21]

Hypotension	Lercanidipine ± Propranolol	Synergic Effect	1	Y	[22]
	Irbesartan ± Perindopril	PD	1	Y	[23,24]
	Ramipril ± Losartan	PD	24	?	[23,24]
	Sildenafil ± Furosemide	Synergic Effect	7	Y	[25]
	Amitriptyline ± Propranolol	Synergic Effect	1	Y	[26]
	Nebivolol ± Doxazosin	Synergic Effect	1	Y	[27]
	Bisoprolol ± Alfuzosin	Synergic Effect	1	Y	[27]
	Bisoprolol ± Doxazosin	Synergic Effect	1	Y	[27]
	Nebivolol ± Tamsulosin	Synergic Effect	108	?	[27]

? = it is not possible to define if it is temporally plausible

AE: Adverse Event; DDI: Drug-Drug interaction; PD: Pharmacodynamic interaction; Y: Yes.

References

1. LeWinter MM, Crawford MH, O'Rourke RA, Karliner JS. The effects of oral propranolol, digoxin and combination therapy on the resting and exercise electrocardiogram. Am Heart J. 1977;93:202–9.

2. Boyer EW, Shannon M. The Serotonin Syndrome. New England Journal of Medicine [Internet]. 2005 [cited 2023 Aug 12];352:1112–20. Available from: https://doi.org/10.1056/NEJMra041867

3. Sala M, Vicentini A, Brambilla P, Montomoli C, Jogia JR, Caverzasi E, et al. QT interval prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy. Ann Gen Psychiatry. 2005;4:1.

4. Park D-W, Kwon O, Jang J-S, Yun S-C, Park H, Kang D-Y, et al. Clinically Significant Bleeding With Ticagrelor Versus Clopidogrel in Korean Patients With Acute Coronary Syndromes Intended for Invasive Management: A Randomized Clinical Trial. Circulation. 2019;140:1865–77.

5. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.

6. Gerlach AT, Pickworth KK, Seth SK, Tanna SB, Barnes JF. Enoxaparin and bleeding complications: a review in patients with and without renal insufficiency. Pharmacotherapy. 2000;20:771–5.

7. Pfizer. Eliquis, Monograph. 2015.

8. Mylan Institutional LLC. Arixtra (Fondaparinux). 2020.

9. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50:e344–418.

10. Kam W, Holmes DN, Hernandez AF, Saver JL, Fonarow GC, Smith EE, et al. Association of Recent Use of Non-Vitamin K Antagonist Oral Anticoagulants With Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Treated With Alteplase. JAMA. 2022;327:760–71.

11. Shahjouei S, Tsivgoulis G, Goyal N, Sadighi A, Mowla A, Wang M, et al. Safety of Intravenous Thrombolysis Among Patients Taking Direct Oral Anticoagulants: A Systematic Review and Meta-Analysis. Stroke. 2020;51:533–41.

12. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. CMAJ. 2013;185:E121-127.

13. Ozturk M, Ipekci A, Kiyak SK, Akdeniz YS, Aydin Y, Ikizceli I, et al. Bleeding Complications in Warfarin-Treated Patients Admitted to the Emergency Department. J Clin Med Res. 2019;11:106–13.

14. Lidell C, Svedberg L-E, Lindell P, Bandh S, Job B, Wallentin L. Clopidogrel and warfarin: absence of interaction in patients receiving long-term anticoagulant therapy for non-valvular atrial fibrillation. Thromb Haemost. 2003;89:842–6.

15. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315–52.

16. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e44S-e88S.

17. Schjerning Olsen A-M, Gislason GH, McGettigan P, Fosbøl E, Sørensen R, Hansen ML, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA. 2015;313:805–14.

18. Fralick M, Macdonald EM, Gomes T, Antoniou T, Hollands S, Mamdani MM, et al. Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study. BMJ. 2014;349:g6196.

19. Crellin E, Mansfield KE, Leyrat C, Nitsch D, Douglas IJ, Root A, et al. Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients: cohort study. BMJ. 2018;360:k341.

20. Mannheimer B, Falhammar H, Calissendorff J, Skov J, Lindh JD. Time-dependent association between selective serotonin reuptake inhibitors and hospitalization due to hyponatremia. J Psychopharmacol. 2021;35:928–33.

21. Raj R, Jacob A, Venkatanarayan A, Doraiswamy M, Ashok M. Severe Symptomatic Hyponatremia Secondary to Escitalopram-Induced SIADH: A Case Report with Literature Review. Case Rep Nephrol. 2018;2018:3697120.

22. Leon MB, Rosing DR, Bonow RO, Epstein SE. Combination therapy with calcium-channel blockers and beta blockers for chronic stable angina pectoris. Am J Cardiol. 1985;55:69B-80B.

23. PRAC recommends against combined use of medicines affecting the renin-angiotensin (RAS) system.

24. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892–903.

25. Rosenkranz S, Erdmann E. [Interaction between sildenafil and antihypertensive drugs: what is evidence-based?]. Dtsch Med Wochenschr. 2001;126:1144–9.

26. Kadioglu SB, Celik T. Orthostatic Hypotension and Drugs: Drug-Induced Orthostatic Hypotension. Orthostatic Hypotension in Older Adults. 2021;45–59.

27. Oelke M, Gericke A, Michel MC. Cardiovascular and ocular safety of α1-adrenoceptor antagonists in the treatment of male lower urinary tract symptoms. Expert Opin Drug Saf. 2014;13:1187–97.

Supplementary Table S2 Plausible confounders related with the time of co-exposure

AE	DDI	Confounders	AEs of interest	Every other AEs	P
Bradycardia	Digoxin ± Bisoprolol	Apixaban Atorvastatin Sacubitril/Valsartan	0 0 0	12 14 12	0.025 0.013 0.025
Confusional state	Amitriptyline ± Duloxetine	**Clonazepam** Pregabalin Mean age	10 0 48.2	1 15 48.3	**0.001** 0.113 0.985
Haemorrhage	Enoxaparin ± Ticagrelor	-	-	-	-
	Ticagrelor ± Heparin	-	-	-	-
	Enoxaparin ± Clopidogrel	Lorazepam Mean age	0 73.8	25 71.9	0.001 0.161
	Apixaban ± Ticagrelor	-	-	-	-
	Apixaban ± Prasugrel	-	-	-	-
	Fondaparinux ± Ticagrelor	Acute coronary syndrome Acute left ventricular failure Analgesic therapy Angina pectoris Cerebrovascular accident prophylaxis Chest pain Off label use Thrombosis prophylaxis **Acetylsalicylic Acid** Ramipril	14 9 9 24 9 4 2 1 24 2	2 0 0 9 0 0 0 3 2 0	0.264 0.126 0.126 0.810 0.126 0.543 1.000 0.068 **0.002** 1.000
	Fondaparinux ± Clopidogrel	-	-	-	-
	Warfarin ± Rivaroxaban	Carvedilol Metoprolol Female	0 4 18	5 1 17	0.012 0.715 0.117

	Ibuprofen ± Clopidogrel	Furosemide	0	2	0.668
Hyponatraemia	Duloxetine ± Escitalopram	Female	0	6	0.084
Hypotension	Lercanidipine ± Propranolol	-	-	-	-
	Irbesartan ± Perindopril	-	-	-	-
	Sildenafil ± Furosemide	-	-	-	-
	Amitriptyline ± Propranolol	Acetaminophen/Codeine	0	6	0.208
		Calcium Carbonate	0	6	0.208
		Lansoprazole	1	3	1.000
		Tramadol	3	1	0.140
	Nebivolol ± Doxazosin	Ramipril	0	2	0.292
		Female	6	4	1.000
	Bisoprolol ± Alfuzosin	Apixaban	0	10	0.006
		Carbidopa/Levodopa	4	0	**0.041**
		Cefuroxime	0	10	0.005
		Dutasteride	4	0	**0.041**
		Ezetimibe	0	10	0.005
		Furosemide	0	2	0.642
		Glyburide/Metformin	0	2	0.642
		Hydrochlorothiazide /Olmesartan	0	2	0.642
	Bisoprolol ± Doxazosin	Acetylsalicylic Acid	0	8	0.068
		Cefalexin	0	7	0.099
		Naproxen	0	7	0.099
		Warfarin	0	12	0.014
		Mean Age	54.7	66.5	**0.011**

Significant concomitant factors in bold for the AE of interest.
AE: Adverse Event; DDI: Drug-Drug interaction

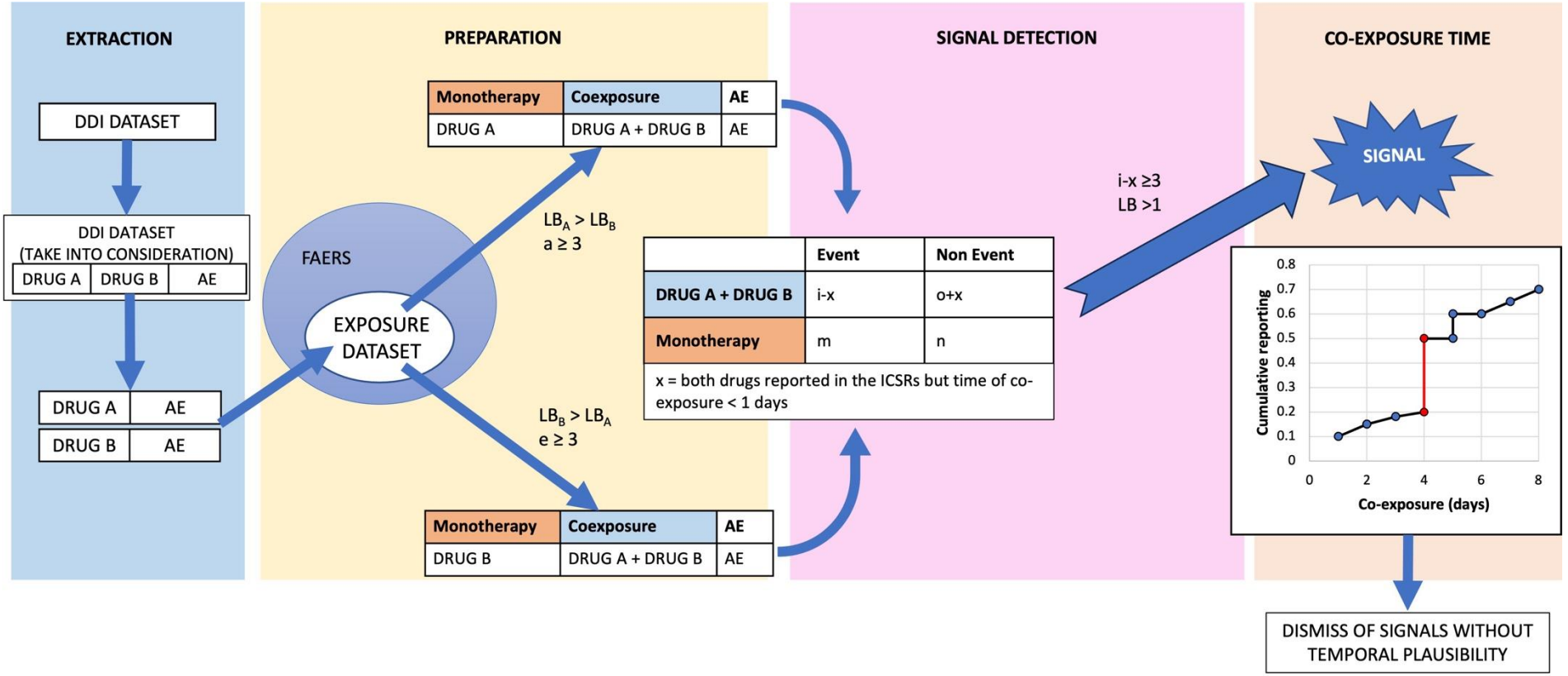

Fig. S1 Description of the process

AE Adverse event, DDI Drug-drug interaction, FAERS Food and Drug Administration Adverse Event Reporting System, LB lower bound

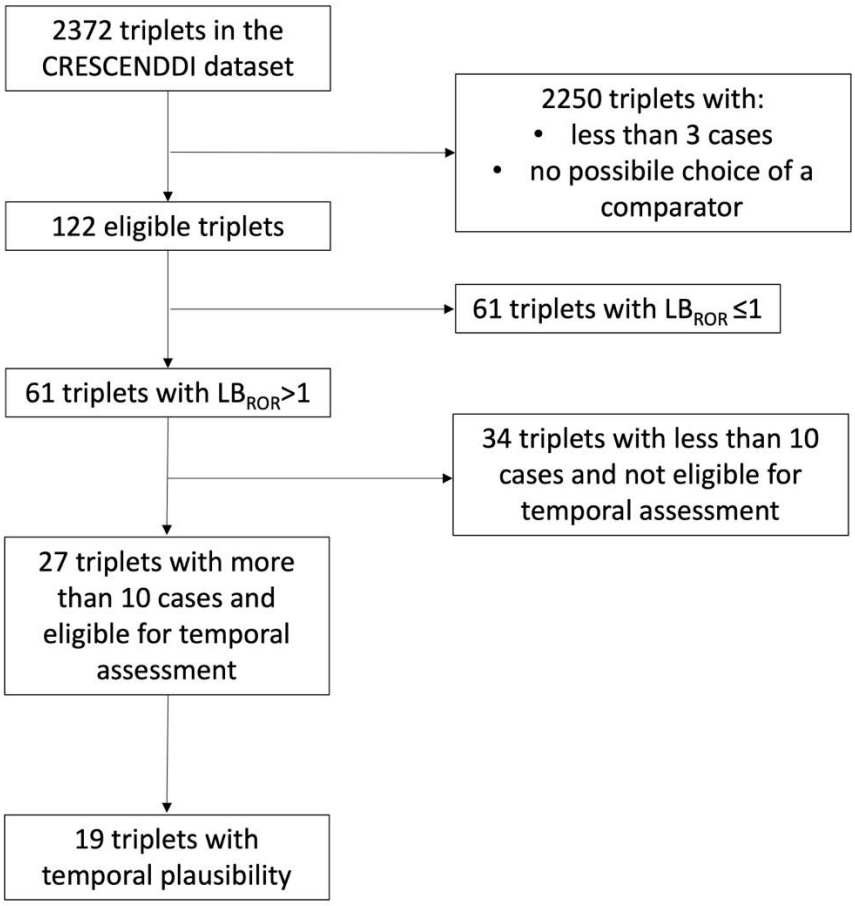

Fig. S2 Flow chart depicting the prioritization method for temporal plausibility assessment of disproportionality signals for DDIs

LB lower bound, ROR reporting Odds Ratio