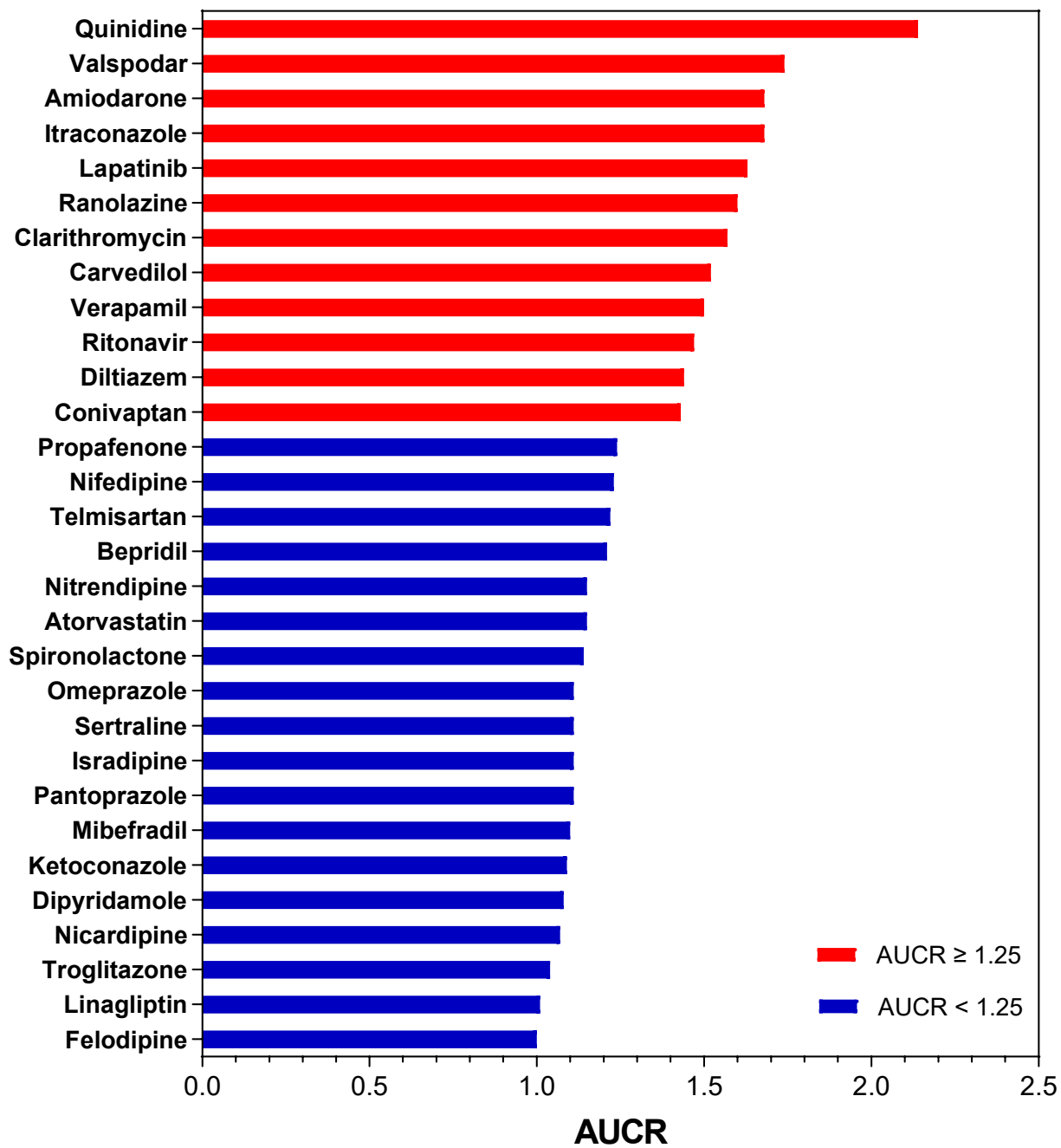


SUPPLEMENTAL FILE 3

Clinical Digoxin Drug-Drug Interactions

Drug	Subjects	n	Inhibitor Dose	Digoxin Dose	AUCR	Reference
Amiodarone	patients	10	400	nl	1.68	1
Atorvastatin	healthy	11	80	0.25	1.15	2
Bepridil	healthy	23	300	0.25	1.21	3
Carvedilol	patients	8	25	0.125-0.25	1.52	4
Clarithromycin	nl	20	500	0.5	1.57	5
Conivaptan	healthy	12	40	0.25	1.43	6
Diltiazem	patients	8	180	0.25	1.44	7
Dipyridamole	healthy	12	75	0.5	1.08	8
Felodipine	healthy	6	10	0.25	1.00	9
Isradipine	healthy	9	2.5-5	0.2	1.11	10
Itraconazole	healthy	10	200	0.5	1.68	11
Ketoconazole	healthy	10	200	0.5	1.09	12
Lapatinib	patients	17	1500	0.5	1.63	13
Linagliptin	healthy	20	5	0.25	1.01	14
Mibefradil	healthy	40	100	0.375	1.10	15
Nicardipine	patients	20	30	0.25-0.5	1.07	16
Nifedipine	healthy	7	10	0.25	1.23	17
Nitrendipine	healthy	8	20	0.25	1.15	18
Omeprazole	healthy	10	20	1	1.11	19
Pantoprazole	healthy	18	40	2	1.11	20
Propafenone	healthy	8	150	0.5	1.24	21
Quinidine	healthy	5	200	nl	2.14	22
Ranolazine	healthy	16	1000	0.125	1.60	23
Ritonavir	nl	8	400	0.25	1.47	24
Sertraline	healthy	20	50	0.25	1.11	25
Spironolactone	healthy	6	100	0.5-1.0	1.14	26
Telmisartan	healthy	12	120	0.25	1.22	27
Troglitazone	healthy	11	400	0.25	1.04	28
Valspodar	healthy	12	200	0.125	1.74	29
Verapamil	healthy	9	80	0.25	1.50	10

Dose = mg, nl = not listed



References:

1. Robinson K, Johnston A, Walker S, Mulrow JP, McKenna WJ, Holt DW. 1989. The digoxin-amiodarone interaction. *Cardiovasc Drugs Ther.* 3(1):25-28.
2. Boyd RA, Stern RH, Stewart BH, Wu X, Reyner EL, Zegarac EA, Randinitis EJ, Whitfield L. 2000. Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. *J Clin Pharmacol.* 40(1):91-98.
3. Doose DR, Wallen S, Nayak RK, Minn FL. 1987. Pharmacokinetic interaction of bepridil and digoxin at steady-state. *Clin Pharmacol Ther.* 41(2):204-204.
4. Souza FC, Neri JS, Marques EB, Barros RBM, Scaramello CBV. 2015. Should pharmacotherapy of digoxin be reviewed in male patients with heart failure in the case of association with carvedilol? *Int J Cardiol.* 191:4-6.
5. Gurley BJ, Swain A, Williams DK, Barone G, Battu SK. 2008. Gauging the clinical significance of P-glycoprotein-mediated herb-drug interactions: comparative effects of St. John's wort, Echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. *Mol Nutr Food Res.* 52(7):772-779.
6. Ali F, Raufi MA, Washington B, Ghali JK. 2007. Conivaptan: a dual vasopressin receptor v1a/v2 antagonist. *Cardiovasc Drug Rev.* 25(3):261-279.
7. Mahgoub AA, El-Medany AH, Abdulatif AS. 2002. A comparison between the effects of diltiazem and isosorbide dinitrate on digoxin pharmacodynamics and kinetics in the treatment of patients with chronic ischemic heart failure. *Saudi Med J.* 23(6):725-731.
8. Verstuyft C, Strabach S, El-Morabet H, Kerb R, Brinkmann U, Dubert L, Jaillon P, Funck-Brentano C, Trugnan G, Becquemont L. 2003. Dipyridamole enhances digoxin bioavailability via P-glycoprotein inhibition. *Clin Pharmacol Ther.* 73(1):51-60.
9. Snyder BD, Rowland A, Polasek TM, Miners JO, Doogue MP. 2014. Evaluation of felodipine as a potential perpetrator of pharmacokinetic drug-drug interactions. *Eur J Clin Pharmacol.* 70(9):1115-22.
10. Rodin SM, Johnson BF, Wilson J, Ritchie P, Johnson J. 1988. Comparative effects of verapamil and isradipine on steady-state digoxin kinetics. *Clin Pharmacol Ther.* 43(6):668-672.
11. Jalava KM, Partanen J, Neuvonen PJ. 1997. Itraconazole decreases renal clearance of digoxin. *Ther Drug Monit.* 19(6):609-613.
12. Larsen UL, Hyldahl Olesen L, Guldberg Nyvold C, Eriksen J, Jakobsen P, Østergaard M, Autrup H, Andersen V. 2007. Human intestinal P-glycoprotein activity estimated by the model substrate digoxin. *Scand J Clin Lab Invest.* 67(2):123-134.
13. Koch KM, Smith DA, Botbyl J, Arya N, Briley LP, Cartee L, White JH, Beyer J, Dar MM, Chung HC, *et al.* 2015. Effect of lapatinib on oral digoxin absorption in patients. *Clin Pharmacol Drug Dev.* 4(6):449-453.
14. Friedrich C, Ring A, Brand T, Sennewald R, Graefe-Mody EU, Woerle HJ. 2011. Evaluation of the pharmacokinetic interaction after multiple oral doses of linagliptin and digoxin in healthy volunteers. *Eur J Drug Metab Pharmacokinet.* 36(1):17-24.
15. Peters J, Welker HA, Bullingham R. 1999. Pharmacokinetic and pharmacodynamic aspects of concomitant mibefradil-digoxin therapy at therapeutic doses. *Eur J Drug Metab Pharmacokinet.* 24(2):133-140.
16. Debruyne D, Commeau P, Grollier G, Huret B, Scanu P, Moulin M. 1989. Nicardipine does not significantly affect serum digoxin concentrations at the steady state of patients with

- congestive heart failure. *Int J Clin Pharmacol Res.* 9(1):15-19.
17. Kirch W, Hutt HJ, Dylewicz P, Gräf KJ, Ohnhaus EE. 1986. Dose-dependence of the nifedipine-digoxin interaction? *Clin Pharmacol Ther.* 39(1):35-39.
 18. Kirch W, Logemann C, Heidemann H, Santos SR, Ohnhaus EE. 1987. Nitrendipine/digoxin interaction. *J Cardiovasc Pharmacol.* 10(Suppl 10):S74-75.
 19. Oosterhuis B, Jonkman JH, Andersson T, Zuiderwijk PBM, Jedema JN. 1991. Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. *Br J Clin Pharmacol* 32: 569-572.
 20. Hartmann M, Huber R, Bliesath H, Steinijans VW, Koch HJ, Wurst W, Kunz K. 1995. Lack of interaction between pantoprazole and digoxin at therapeutic doses in man. *Int J Clin Pharmacol Ther.* 33(9):481-485.
 21. Cardaioli P, Compostella L, De Domenico R, Papalia D, Zeppellini R, Libardoni M, Pulido E, Cucchini F. 1986. Effect of propafenone on the pharmacokinetics of digoxin administered orally: a study in healthy volunteers. *G Ital Cardiol.* 16(3):237-240.
 22. Fenster PE, Powell RJ, Hager WD, Graves PE, Conrad K, Goldman S. 1980. Onset and dose dependence of the digoxin-quinidine interaction. *Am J Cardiol.* 45 (2):413.
 23. Jerling M. 2006. Clinical pharmacokinetics of ranolazine. *Clin Pharmacokinet.* 45(5):469-491.
 24. Kirby BJ, Collier AC, Kharasch ED, Whittington D, Thummel KE, Unadkat JD. 2012. Complex drug interactions of the HIV protease inhibitors 3: effect of simultaneous or staggered dosing of digoxin and ritonavir, nelfinavir, rifampin, or bupropion. *Drug Metab Dispos.* 40(3):610-616.
 25. Rapeport WG, Coates PE, Dewland PM, Forster PL. 1996. Absence of a sertraline-mediated effect on digoxin pharmacokinetics and electrocardiographic findings. *J Clin Psychiatry.* 57(Suppl 1):16-19.
 26. Hedman A, Angelin B, Arvidsson A, Dahlqvist R. 1992. Digoxin-interactions in man: spironolactone reduces renal but not biliary digoxin clearance. *Eur J Clin Pharmacol.* 42(5):481-485.
 27. Stangier J, Su CA, Hendriks MG, van Lier JJ, Sollie FA, Oosterhuis B, Jonkman JH. 2000. The effect of telmisartan on the steady-state pharmacokinetics of digoxin in healthy male volunteers. *J Clin Pharmacol.* 40(12 Pt 1):1373-1379.
 28. Loi CM, Knowlton PW, Stern R, Randinitis EJ, Vassos AB, Koup JR, Sedman AJ. 1998. Effect of troglitazone on steady-state pharmacokinetics of digoxin. *J Clin Pharmacol.* 38(2):178-83.
 29. Kovarik JM, Rigaudy L, Guerret M, Gerbeau C, Rost KL. 1999. Longitudinal assessment of a P-glycoprotein-mediated drug interaction of valspodar on digoxin. *Clin Pharmacol Ther.* 66(4):391-400.

Dose Information for Inhibitor Drugs

Drug	HDP A	Reference
Amiodarone	400	1
Atorvastatin	80	2
Bepridil	400	3
Carvedilol	25	4
Clarithromycin	500	5
Conivaptan	20	6
Diltiazem	120	7
Dipyridamole	100	8
Felodipine	10	9
Isradipine	10	10
Itraconazole	200	11
Ketoconazole	400	12
Lapatinib	1250	13
Linagliptin	5	14
Mibefradil	100	15
Nicardipine	40	16
Nifedipine	30	17
Nitrendipine	40	18
Omeprazole	40	19
Pantoprazole	40	20
Propafenone	300	21
Quinidine	300	22
Ranolazine	1000	23
Ritonavir	600	24
Sertraline	200	25
Spironolactone	100	26
Telmisartan	80	27
Troglitazone	600	28
Valspodar	600	29
Verapamil	120	30

HDP A = highest dose per administration (mg)

References:

1. CORDARONE® (amiodarone) tablets, for oral use. Wyeth Pharmaceuticals Inc. Philadelphia, PA. Revised 10/2018.
2. LIPITOR® (atorvastatin calcium) tablets, for oral use. Parke-Davis. New York, NY. Revised. 11/2020.
3. www.rxlist.com/vascor-drug.htm
4. COREG (carvedilol) tablets for oral use. GlaxoSmithKline. Research Triangle Park, NC. Revised 09/2017.
5. BIAXIN® Filmtab® (clarithromycin) tablets, for oral use. AbbVie Inc., North Chicago, IL. Revised 09/2019.
6. VAPRISOL® (conivaptan hydrochloride) injection, for intravenous use. Cumberland Pharmaceuticals Inc. Nashville TN. Revised 10/2016.
7. CARDIZEM® (diltiazem hydrochloride) tablets. Bausch Health Companies Inc. Bridgewater, NJ. Revised 06/2020.
8. Persantine® (dipyridamole USP) tablets. Boehringer Ingelheim. Revised 12/2019.
9. PLENDIL® (felodipine) extended-release tablets. AstraZeneca LP. Wilmington, DE. Revised 10/2012.
10. ISRADIPINE- isradipine capsule. Actavis Pharma, Inc. Parsippany, NJ. Revised 06/2017.
11. SPORANOX® (itraconazole) capsules. Janssen Pharmaceuticals, Inc. Titusville, NJ. Revised 03/2019.
12. NIZORAL® (ketoconazole) tablets. Janssen Pharmaceuticals, Inc. Titusville, NJ. Revised 02/2014.
13. TYKERB® (lapatinib) tablets, for oral use. Novartis Pharmaceuticals Corporation East Hanover, NJ. Revised 12/2018.
14. TRADJENTA® (linagliptin tablets), for oral use. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. Revised 03/2020.
15. Brogden RN, Markham A. 1997. Mibefradil. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the management of hypertension and angina pectoris. *Drugs*. 54(5):774-793.
16. CARDENE® (nicardipine hydrochloride) capsules. Roche Laboratories Inc. Nutley. NJ. Revised 08/2016.
17. PROCARDIA® (nifedipine) capsules. Pfizer Labs. New York, NY. Revised 01/2015.
18. Goa KL, Sorkin EM. Nitrendipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of hypertension. *Drugs*. 1987; 33(2):123-155.
19. PRILOSEC® (omeprazole) delayed-release capsules. AstraZeneca Pharmaceuticals LP, Wilmington, DE. Revised 12/2016.
20. PROTONIX® (pantoprazole sodium) delayed-release tablets, for oral use. Wyeth Pharmaceuticals LLC. Philadelphia, PA. Revised 11/2020.
21. RYTHMOL(propafenone hydrochloride tablets), for oral use. GlaxoSmithKline. Research Triangle Park, NC. Revised 11/2018.
22. Quinidex Extentabs® tablets. (quinidine sulfate extended release tablets, USP). A.H. Robins Company. Richmond, VA. Revised 09/2000.
23. RANEXA® (ranolazine) extended-release tablets, for oral use. Gilead Sciences, Inc. Foster City, CA. Revised 10/2019.

24. NORVIR (ritonavir) tablets, for oral use. AbbVie Inc., North Chicago, IL. Revised 10/2020.
25. ZOLOFT (sertraline hydrochloride) tablets, for oral use. Roerig. New York, NY. Revised 12/2017.
26. ALDACTONE® (spironolactone) tablets for oral use. G.D. Searle LLC. New York, NY. Revised 06/2020.
27. MICARDIS® (telmisartan) tablets, for oral use. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. Revised 02/2018.
28. REZULIN® (troglitazone) tablets. Parke-Davis. Morris Plains, NJ. Revised 06/1999.
29. Mueller EA, Kovarik JM, Üresin Y, Preisig-Flückiger SS, Hensel S, Lücker PW, Holt B. 1997. Optimizing the absorption of valspodar, a P-glycoprotein modulator, Part I: Selecting an oral formulation and exploring its clinical pharmacokinetics/dynamics. J Clin Pharmacol. 37(11):1001-10008.
30. CALAN® verapamil hydrochloride tablets. G.D. Searle LLC. New York, NY. Revised 09/2017.

Drug product labels from Drugs@FDA [<https://www.accessdata.fda.gov/scripts/cder/daf/>]