

Drug Safety

Risk of out-of-hospital sudden cardiac death in users of domperidone, users of proton pump inhibitors, and users of metoclopramide: a population-based nested case-control study

Electronic supplementary material

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Table S1. Incidence per 1,000 person-years of sudden cardiac death in the exposure cohort, overall and stratified analyses, N = 681,104

	Number of SCD cases	Number of person-years	Incidence rate per 1,000 person-years	95% CI
Total study cohort				
Total	3,282	2,112,381.64	1.55	(1.50 to 1.61)
Male	1,917	904,678.90	2.12	(2.03 to 2.22)
Female	1,365	1,207,702.74	1.13	(1.07 to 1.19)
Age group (years)				
2-15	0	18,644.41	0.00	(0.00 to 0.20)
16-25	1	95,866.23	0.01	(0.00 to 0.06)
26-35	7	165,691.27	0.04	(0.02 to 0.09)
36-45	50	301,892.44	0.17	(0.12 to 0.22)
46-55	164	373,750.74	0.44	(0.37 to 0.51)
56-65	375	426,150.32	0.88	(0.79 to 0.97)
66-75	668	377,709.35	1.77	(1.64 to 1.91)
76-85	1,092	263,286.30	4.15	(3.91 to 4.40)
> 85	925	89,390.59	10.35	(9.69 to 11.04)
Diabetes mellitus^a				
None	2,633	1,957,911.16	1.34	(1.29 to 1.40)
Severity level 1	516	128,705.62	4.01	(3.67 to 4.37)
Severity level 2	133	25,719.11	5.17	(4.33 to 6.13)

	Number of SCD cases	Number of person-years	Incidence rate per 1,000 person-years	95% CI
Domperidone current use^b				
Total	90	20,153.10	4.47	(3.59 to 5.49)
Male	34	6,842.90	4.97	(3.44 to 6.94)
Female	56	13,310.20	4.21	(3.18 to 5.46)
Age group (years)				
2-15	0	725.00	0.00	(0.00 to 5.09)
16-25	0	868.47	0.00	(0.00 to 4.25)
26-35	1	1,094.02	0.91	(0.02 to 5.09)
36-45	0	2,031.82	0.00	(0.00 to 1.82)
46-55	3	2,926.74	1.03	(0.21 to 3.00)
56-65	12	3,983.13	3.01	(1.56 to 5.26)
66-75	12	4,087.52	2.94	(1.52 to 5.13)
76-85	26	3,171.63	8.20	(5.35 to 12.01)
> 85	36	1,264.77	28.46	(19.94 to 39.41)
Diabetes mellitus^a				
None	69	18,007.26	3.83	(2.98 to 4.85)
Severity level 1	14	1,619.09	8.65	(4.73 to 14.51)
Severity level 2	7	526.70	13.29	(5.34 to 27.38)

	Number of SCD cases	Number of person-years	Incidence rate per 1,000 person-years	95% CI
PPI current use^b				
Total	2,064	778,229.45	2.65	(2.54 to 2.77)
Male	1,195	352,877.10	3.39	(3.20 to 3.58)
Female	869	425,352.34	2.04	(1.91 to 2.18)
Age group (years)				
2-15	0	1,647.26	0.00	(0.00 to 2.24)
16-25	0	7,758.51	0.00	(0.00 to 0.48)
26-35	3	24,150.11	0.12	(0.03 to 0.36)
36-45	31	68,915.69	0.45	(0.31 to 0.64)
46-55	97	116,436.70	0.83	(0.68 to 1.02)
56-65	226	179,067.85	1.26	(1.10 to 1.44)
66-75	409	186,337.26	2.19	(1.99 to 2.42)
76-85	670	141,926.41	4.72	(4.37 to 5.09)
> 85	628	51,989.65	12.08	(11.15 to 13.06)
Diabetes mellitus^a				
None	1,664	697,536.64	2.39	(2.27 to 2.50)
Severity level 1	310	67,835.84	4.57	(4.08 to 5.11)
Severity level 2	90	12,821.04	7.02	(5.64 to 8.63)

	Number of SCD cases	Number of person-years	Incidence rate per 1,000 person-years	95% CI
Metoclopramide current use^b				
Total	83	16,046.15	5.17	(4.12 to 6.41)
Male	34	4,973.88	6.84	(4.73 to 9.55)
Female	49	11,072.26	4.43	(3.27 to 5.85)
Age group (years)				
2-15	0	213.08	0.00	(0.00 to 17.31)
16-25	0	772.75	0.00	(0.00 to 4.77)
26-35	0	1,225.39	0.00	(0.00 to 3.01)
36-45	3	2,101.38	1.43	(0.29 to 4.17)
46-55	4	2,792.48	1.43	(0.39 to 3.67)
56-65	10	3,209.30	3.12	(1.49 to 5.73)
66-75	16	2,804.51	5.71	(3.26 to 9.26)
76-85	24	2,146.16	11.18	(7.17 to 16.64)
> 85	26	781.09	33.29	(21.74 to 48.77)
Diabetes mellitus ^a				
None	64	14,423.75	4.44	(3.42 to 5.67)
Severity level 1	14	1,224.82	11.43	(6.25 to 19.18)
Severity level 2	5	397.57	12.58	(4.08 to 29.35)

	Number of SCD cases	Number of person-years	Incidence rate per 1,000 person-years	95% CI
Non-use of study drug				
Total	1,151	1,318,758.17	0.87	(0.82 to 0.92)
Male	694	547,276.73	1.27	(1.18 to 1.37)
Female	457	771,481.44	0.59	(0.54 to 0.65)
Age group (years)				
2-15	0	16,347.76	0.00	(0.00 to 0.23)
16-25	1	86,926.20	0.01	(0.00 to 0.06)
26-35	4	140,007.65	0.03	(0.01 to 0.07)
36-45	18	230,876.84	0.08	(0.05 to 0.12)
46-55	65	254,925.52	0.25	(0.20 to 0.32)
56-65	140	244,442.72	0.57	(0.48 to 0.68)
66-75	246	189,008.25	1.30	(1.14 to 1.47)
76-85	402	119,518.34	3.36	(3.04 to 3.71)
> 85	275	36,704.88	7.49	(6.63 to 8.43)
Diabetes mellitus ^a				
None	918	1,246,327.22	0.74	(0.69 to 0.79)
Severity level 1	192	59,869.21	3.21	(2.77 to 3.69)
Severity level 2	41	12,551.96	3.27	(2.34 to 4.43)

CI confidence interval, PPI proton pump inhibitor, SCD sudden cardiac death.

^a Severity level 1: diagnosis only; severity level 2: diagnosis + insulin or complication.

^b Current use of each study medication could include use of any other study medication.

Table S2. Exposure status at the index date for nested case-control analysis

Case/control status	Exposure category	Number of subjects
Case		
	Current exposure to domperidone alone	28
	Current exposure to PPI alone	1,935
	Current exposure to metoclopramide alone	37
	Current combined exposure	
	Domperidone + PPI	51
	Domperidone + metoclopramide	0
	PPI + metoclopramide	41
	Domperidone + PPI + metoclopramide	4
	Past exposure to any study drug	341
	No exposure to any study drug	802
Control		
	Current exposure to domperidone alone	52
	Current exposure to PPI alone	6,499
	Current exposure to metoclopramide alone	44
	Current combined exposure	
	Domperidone + PPI	90
	Domperidone + metoclopramide	0
	PPI + metoclopramide	60
	Domperidone + PPI + metoclopramide	4
	Past exposure to any study drug	1,330
	No exposure to any study drug	4,493

PPI proton pump inhibitor.

Table S3. Distribution of covariates among 3,239 cases and 12,572 controls and unadjusted odds ratio for sudden cardiac death, results of unadjusted conditional logistic regression

Variable	SCD cases		Controls		Odds ratio matched for age, sex, and medical practice	95% CI
	N	%	N	%		
Diabetes mellitus						
None	2,521	77.8	10,761	85.6		
Diagnosis only	558	17.2	1,546	12.3	1.60	(1.44 to 1.78)
Diagnosis + insulin or complication	160	4.9	265	2.1	2.71	(2.21 to 3.33)
History of serious ventricular arrhythmia	69	2.1	92	0.7	3.03	(2.21 to 4.16)
Autonomic neuropathy	19	0.6	33	0.3	2.33	(1.32 to 4.11)
Cerebrovascular disease	609	18.8	1,820	14.5	1.36	(1.23 to 1.51)
Myocardial infarction	896	27.7	1,309	10.4	3.46	(3.12 to 3.82)
Ischaemic heart disease other than myocardial infarction	977	30.2	2,284	18.2	2.01	(1.83 to 2.20)
Coronary revascularization procedure	232	7.2	569	4.5	1.70	(1.44 to 2.00)
Heart failure	806	24.9	1,037	8.2	4.07	(3.64 to 4.54)
Pulmonary heart disease	106	3.3	260	2.1	1.61	(1.28 to 2.03)
Valvular heart disease, including valve replacement	208	6.4	465	3.7	1.83	(1.54 to 2.17)
Cardiomyopathy	37	1.1	54	0.4	2.78	(1.82 to 4.25)
Other arrhythmia or conduction disorder	790	24.4	1,917	15.2	1.83	(1.66 to 2.02)
Electrophysiology procedures for treatment of arrhythmias	166	5.1	333	2.6	1.93	(1.59 to 2.35)
Renal impairment	327	10.1	671	5.3	2.02	(1.75 to 2.33)
Hypertension	1,804	55.7	6,313	50.2	1.27	(1.17 to 1.38)
Hypercholesterolemia/ Hyperlipidemia	695	21.5	2,272	18.1	1.30	(1.17 to 1.44)
Severe chronic obstructive pulmonary disease	75	2.3	236	1.9	1.26	(0.96 to 1.64)

Variable	SCD cases		Controls		Odds ratio matched for age, sex, and medical practice	95% CI
	N	%	N	%		
Asthma	581	17.9	2,029	16.1	1.15	(1.04 to 1.27)
Epilepsy	95	2.9	250	2.0	1.52	(1.20 to 1.94)
Depression	791	24.4	2,605	20.7	1.27	(1.15 to 1.39)
Schizophrenia	37	1.1	46	0.4	3.20	(2.07 to 4.95)
Dyspepsia	736	22.7	3,465	27.6	0.76	(0.69 to 0.83)
Gastric or peptic ulcer	338	10.4	1,163	9.3	1.15	(1.01 to 1.31)
Gastritis and duodenitis	365	11.3	1,395	11.1	1.02	(0.90 to 1.16)
Gastro-oesophageal reflux disease	379	11.7	1,802	14.3	0.78	(0.69 to 0.88)
Disorder of stomach/duodenum (other than dyspepsia)	35	1.1	158	1.3	0.85	(0.58 to 1.23)
Liver failure	3	0.1	11	0.1	1.09	(0.30 to 3.91)
Hepatic impairment	67	2.1	171	1.4	1.58	(1.18 to 2.10)
Parkinson's disease	59	1.8	179	1.4	1.28	(0.95 to 1.73)
QTc-prolonging drugs, group 1 ^a						
No exposure	2,404	74.2	10,238	81.4		
Current exposure	402	12.4	855	6.8	2.02	(1.78 to 2.30)
Past exposure	433	13.4	1,479	11.8	1.26	(1.12 to 1.41)
QTc-prolonging drugs, group 2 ^a						
No exposure	2,873	88.7	11,426	90.9		
Current exposure	207	6.4	648	5.2	1.29	(1.09 to 1.52)
Past exposure	159	4.9	498	4.0	1.26	(1.05 to 1.52)
Strong CYP3A4 inhibitors						
No exposure	3,003	92.7	11,847	94.2		
Current exposure	40	1.2	88	0.7	1.73	(1.18 to 2.53)
Past exposure	196	6.1	637	5.1	1.23	(1.04 to 1.46)

Variable	SCD cases		Controls		Odds ratio matched for age, sex, and medical practice	95% CI
	N	%	N	%		
Weak CYP3A4 inhibitors						
No exposure	2,633	81.3	11,063	88.0		
Current exposure	287	8.9	600	4.8	2.06	(1.78 to 2.40)
Past exposure	319	9.8	909	7.2	1.50	(1.31 to 1.72)
CYP3A4 inducers						
No exposure	2,424	74.8	10,208	81.2		
Current exposure	417	12.9	1,025	8.2	1.74	(1.54 to 1.97)
Past exposure	398	12.3	1,339	10.7	1.27	(1.12 to 1.43)
Drugs that affect <i>hERG</i>						
No exposure	1,889	58.3	8,138	64.7		
Current exposure	726	22.4	1,876	14.9	1.68	(1.52 to 1.86)
Past exposure	624	19.3	2,558	20.3	1.06	(0.96 to 1.17)
Digoxin						
No exposure	2,793	86.2	11,822	94.0		
Current exposure	294	9.1	525	4.2	2.42	(2.08 to 2.83)
Past exposure	152	4.7	225	1.8	2.98	(2.40 to 3.70)
Diuretics						
No exposure	1,350	41.7	8,012	63.7		
Current exposure	1,279	39.5	2,877	22.9	2.91	(2.65 to 3.21)
Past exposure	610	18.8	1,683	13.4	2.31	(2.06 to 2.59)
Laxatives						
No exposure	2,168	66.9	9,353	74.4		
Current exposure	463	14.3	1,313	10.4	1.55	(1.37 to 1.75)
Past exposure	608	18.8	1,906	15.2	1.39	(1.25 to 1.55)

Variable	SCD cases		Controls		Odds ratio matched for age, sex, and medical practice	95% CI
	N	%	N	%		
Systemic beta-adrenergic receptor agonists						
No exposure	3,229	99.7	12,528	99.7		
Current exposure			2	0.0	0.00	(0.00 to 4.668757)
Past exposure	10	0.3	42	0.3	0.95	(0.48 to 1.90)
Oral corticosteroids						
No exposure	2,697	83.3	11,156	88.7		
Current exposure	256	7.9	516	4.1	2.08	(1.78 to 2.44)
Past exposure	286	8.8	900	7.2	1.34	(1.17 to 1.55)
Gastrointestinal medications other than study drugs						
Antihypertensive medications	1,861	57.5	5,420	43.1	1.85	(1.71 to 2.01)
Antiarrhythmic agents with action on repolarization time	235	7.3	698	5.6	1.34	(1.15 to 1.57)
Antiarrhythmic agents without action on repolarization time	247	7.6	635	5.1	1.57	(1.34 to 1.83)
Beta-blockers	1,233	38.1	3,621	28.8	1.55	(1.42 to 1.68)
Other cardiac medications	2,508	77.4	8,076	64.2	2.06	(1.87 to 2.27)
Body mass index						
BMI < 20	271	8.4	788	6.3	1.40	(1.20 to 1.64)
20 ≤ BMI < 25	880	27.2	3,559	28.3		
25 ≤ BMI < 30	967	29.9	4,577	36.4	0.86	(0.78 to 0.95)
30 ≤ BMI < 40	614	19.0	2,396	19.1	1.06	(0.94 to 1.19)
≥ 40	109	3.4	199	1.6	2.27	(1.77 to 2.91)
Missing	398	12.3	1,053	8.4		

Variable	SCD cases		Controls		Odds ratio matched for age, sex, and medical practice	95% CI
	N	%	N	%		
Smoking history						
Current	604	18.6	1,281	10.2	2.57	(2.27 to 2.90)
Former	1,280	39.5	4,951	39.4	1.30	(1.19 to 1.43)
Never	1,312	40.5	6,280	50.0		
Missing	43	1.3	60	0.5		
Alcohol use						
Current	1,938	59.8	8,452	67.2	0.81	(0.73 to 0.90)
Former	178	5.5	560	4.5	1.14	(0.94 to 1.38)
Never	697	21.5	2,486	19.8		
Missing	426	13.2	1,074	8.5		
Number of GP visits						
< 12	891	27.5	4,955	39.4		
12-24	1,140	35.2	4,967	39.5	1.37	(1.24 to 1.51)
> 24	1,208	37.3	2,650	21.1	2.91	(2.62 to 3.25)
Number of hospital admissions						
0	1,772	54.7	8,412	66.9		
1	745	23.0	2,453	19.5	1.45	(1.31 to 1.60)
2	388	12.0	997	7.9	1.88	(1.65 to 2.13)
≥ 3	334	10.3	710	5.6	2.27	(1.97 to 2.62)

BMI body mass index, CI confidence interval, GP general practitioner, hERG human Ether-à-go-go-Related Gene, SCD sudden cardiac death.

^a QTc-prolonging drugs that may cause arrhythmia or prolong the QTc interval were assessed from the most recent lists available from the CredibleMeds website (maintained by AZCERT, Inc.) on September 11, 2013. Group 1 included drugs with a risk of torsades de pointes (TdP) and Group 2 were drugs with a possible risk of TdP.

Table S4. Subgroup analyses by diabetes status and concurrent use of medications

Exposure category (categories are mutually exclusive)	Diabetes status		CYP3A4 inhibitors		QTc-prolonging medications (group 1)	
	None odds ratio (95% CI)	Yes odds ratio (95% CI)	No use odds ratio (95% CI)	Any use odds ratio (95% CI)	No use odds ratio (95% CI)	Any use odds ratio (95% CI)
Current exposure to domperidone	2.53 (1.20 to 5.31)	0.72 (0.04 to 12.00)	1.54 (0.70 to 3.38)	3.61 (0.44 to 29.66)	1.64 (0.73 to 3.72)	4.95 (0.84 to 29.07)
Current exposure to PPI	1.45 (1.26 to 1.66)	1.18 (0.76 to 1.84)	1.41 (1.24 to 1.62)	1.41 (0.84 to 2.36)	1.38 (1.21 to 1.58)	1.25 (0.79 to 1.97)
Current exposure to metoclopramide	3.76 (1.72 to 8.22)	5584131.19 (0.00 to Infinity)	4.85 (2.33 to 10.11)	12668469.1 (0.00 to Infinity)	4.83 (2.31 to 10.11)	6.63 (0.53 to 82.90)
Current combined exposure	3.29 (2.10 to 5.15)	3.03 (0.69 to 13.22)	2.73 (1.71 to 4.37)	13.01 (2.90 to 58.40)	2.04 (1.28 to 3.27)	5.08 (1.24 to 20.80)
Past exposure to any study drug	1.29 (1.04 to 1.59)	0.74 (0.39 to 1.43)	1.16 (0.94 to 1.44)	1.89 (0.90 to 3.95)	1.18 (0.95 to 1.45)	1.74 (0.87 to 3.46)
No exposure to any study drug	Reference	Reference	Reference	Reference	Reference	Reference

CI confidence interval, PPI proton pump inhibitor.