Title: **Loperamide and Brugada syndrome**

Version: 2

Objective: Calculate incidence of Brugada syndrome in patients treated with loperamide products.

Characterise the cases in terms of number of cases, time to onset, age, gender.

Database: THIN_1809

Population: Patients with one year minimum follow-up time in THIN since 2000 and with "acceptable" status (Patflag A or C). No restriction on age.

Period: 2000 onwards (Brugada Syndrome was first described in 1992 and doesn't appear in THIN until 2000). End of collection: 25 September 2018.

Exposure: any prescribing for loperamide (52 drug codes – see Appendix A)

Exclusions: Patients exposed to other drugs associated with Brugada Syndrome within 30 days of exposure to loperamide (see Appendix B).

Outcomes:

Primary: Read code 'G57y200': Brugada syndrome (occurs 513 times in all patients)

Secondary: Right Bundle Branch Block (occurs 8,490 times in all patients):

3299	ECG: right bundle branch block
G564.00	Right bundle branch block
Gyu5W00	[X]Other and unspecified right bundle-branch block

Tertiary: Ventricular tachycardia/fibrillation

Read code	description	number
3282	ECG: ventricular tachycardia	869
3283	ECG: ventricular fibrillation	25
G571.00	Paroxysmal ventricular tachycardia	5474
G571.11	Ventricular tachycardia	3473
G574.00	Ventricular fibrillation and flutter	649
G574000	Ventricular fibrillation	1279
G574011	Cardiac arrest-ventricular fibrillation	502
G574z00	Ventricular fibrillation and flutter NOS	11

Quaternary: Sudden Cardiac Death / Cardiac arrest

G575100	Sudden cardiac death, so described	approx. 800
2241	O/E - collapse -cardiac arrest	1501
G574011	Cardiac arrest-ventricular fibrillation	502
G575.00	Cardiac arrest	12076
G575000	Cardiac arrest with successful resuscitation	551
G575z00	Cardiac arrest, unspecified	128

Method: Crude event rates (with 95% CI) defined as number of patients with events divided by total number of patients exposed.

The duration for time to event was calculated as the shortest time from exposure to event for each patient and then stratified into three categories (< 1 year, 1 to 5 years, > 5 years). For Brugada Syndrome this was summarised as median, minimum & maximum time in days.

Findings:

	Brugada syndrome	Right Bundle Branch Block	Ventricular tachycardia / fibrillation	Sudden Cardiac Death
underlying population	12,302,234			
n events (*n* patients with at least one event)	414 (322)	4,441 (4,204)	6,840 (5,453)	7,797 (7,309)
total prescriptions	3,134,115			
total patients	614,308			
prescribed during study follow-up				
total prescriptions	2,600,683			
total patients	476,072			
after exclusions (co-prescribed meds)				
total prescriptions	2,366,342			
total patients	457,996			
total events after exposure (patients)	12 (9)	391 (364)	584 (475)	778 (752)
within < 1 year	(1)	(83)	(138)	(232)
within 1 to 5 years	(3)	(123)	(173)	(261)
after 5 years	(5)	(158)	(164)	(259)
event rate*				
event rate (per 100,000 patients)	0.22	18.12	30.13	50.66
95% CI	(0.01-1.22)	(14.43-22.47)	(25.31-35.6)	(44.35-57.61)

* occurring within one year

For the nine patients exposed to loperamide who then had subsequent diagnoses of Brugada Syndrome, the median time to event was 1,955 days with a minimum of 5 days and a maximum of 5,100 days. The median age at onset of Brugada Syndrome was 50 years, with minimum 38 and maximum 76. Seven of the nine events (77%) occurred in females.

Summary and discussion:

Brugada Syndrome is only very rarely recorded in THIN and occurs within a year of exposure to loperamide, at a rate of less than one per 100,000 patients exposed. The gender distribution is different from the non- drug induced Brugada syndrome, which is more common in men.

Right Bundle Branch Block is a potential differential diagnosis and is more frequently recorded in THIN; however, it may well reflect pathologies other than Brugada Syndrome. Atypical Right Bundle Branch Block would be preferred but isn't recorded in THIN.

Ventricular tachycardia / fibrillation and sudden cardiac death are both clinical manifestations of Brugada syndrome and are often recorded in THIN, but will have many causes other than Brugada Syndrome.

The dose of loperamide has not been considered in this analysis. This is because the dose is determined according to the patients' symptoms (taken as needed) and there is no (simple) way of knowing what doses patients actually take as any given time.

The Brugada syndrome is too rare to allow drawing a conclusion on its association with loperamide treatment. For the other arrhythmias, an association cannot be excluded, however a proper epidemiological study has to be designed in order to investigate it.

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Date: 5 March 2018

Appendix A. THIN_1809 drug codes used in analysis

drugcode	description	frequency
39754978	Loperamide 2mg capsules	3
46952978	Loperamide 2mg orodispersible tablets sugar free	345
52020978	Loperamide 2mg capsules	121
57010978	Loperamide 2mg orodispersible tablets sugar free	1
57011978	Loperamide 2mg orodispersible tablets sugar free	1422
59423978	Loperamide 2mg orodispersible tablets sugar free	8
59424978	Loperamide 2mg orodispersible tablets sugar free	4706
67054979	Loperamide 2.5mg/5ml oral solution	1
67059979	Loperamide 1mg/5ml oral solution sugar free	8
73285978	Loperamide 2mg capsules	90
73286978	Loperamide 2mg capsules	9
79611979	Loperamide 4mg/5ml oral solution	1
79615979	Loperamide 25mg/5ml oral solution	45
81123998	Loperamide 25mg/5ml oral suspension	180
82016998	Loperamide 2mg capsules	10685
82017998	Loperamide 2mg capsules	10128
83183998	Loperamide 2mg capsules	3550
83351978	Loperamide 2mg capsules	4
83494978	Loperamide 2mg / simeticone 125mg tablets	303
86504998	Loperamide 2mg capsules	21
88039998	Loperamide hydrochloride & simeticone 2mg+125mg chewable tablets	1578
88040998	Simeticone 125mg with loperamide 2mg chewable tablet	29
88041998	Simeticone 125mg / loperamide 2mg chewable tablets	605
88353998	Loperamide 2mg / Simeticone 125mg tablets	3938
88544998	Loperamide 2mg / Simeticone 125mg tablets	4244
88731998	Loperamide hydrochloride 2mg capsules	140
89502997	Loperamide 2mg capsules	15
89570997	Loperamide 1mg/5ml oral solution sugar free	8183
89570998	Loperamide 2mg capsules	32917
89987998	Loperamide 2mg tablets	18
90575998	Loperamide 2mg capsules	16
90715998	Loperamide 2mg tablets	1438
91167998	Loperamide 2mg capsules	516
91224998	Loperamide and oral rehydration salts capsule and sachets	132
92039998	Loperamide 2mg capsules	12
92474998	Loperamide 2mg orodispersible tablets sugar free	2910
92475998	Loperamide 2mg orodispersible tablets sugar free	3247
92476998	Loperamide 2mg orodispersible tablets sugar free	8996
92746998	Loperamide hydrochloride 2mg capsules	763
95996998	Loperamide 1mg/5ml oral solution sugar free	56286
95997997	Loperamide 2mg tablets	171409
95997998	Loperamide 2mg capsules	2471935
96806990	Loperamide 2mg capsules	2

96814998	Loperamide 2mg capsules	2
96854990	Loperamide 2mg capsules	158
98036990	Loperamide 2mg capsules	468
98037990	Loperamide 2mg capsules	588
98963990	Loperamide 2mg capsules	925
98964990	Loperamide 2mg capsules	1336
99505979	Loperamide 2mg capsules	3
99537997	Loperamide 1mg/5ml oral solution sugar free	5688
99537998	Loperamide 2mg capsules	323987

Appendix B. Other drugs known to cause Brugada's syndrome

Antiarrhythmic drugs

- Flecainide
- Procainamide
- Propafenone

Psychotropic drugs

- Amitriptyline
- Clomipramine
- Desipramine
- Lithium
- Loxapine
- Nortriptyline
- Oxcarbazepine
- Trifluoperazine

Anesthetics / analgesics

- Bupivacaine
- Procaine
- Propofol

Other substances

- Cannabis
- Cocaine
- Ergonovine

(taken from: https://www.brugadadrugs.org/avoid/)