

Supplementary file

Title: Systematic assessment of prescribed medications and short-term risk of myocardial infarction – a pharmacoepia-wide association study from Norway and Sweden

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Supplementary file

Table S1 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed. Univariable and BOLASSO results for drugs selected by BOLASSO approach in Norway.

Table S2 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed. Univariable and BOLASSO results for drugs selected by BOLASSO approach in Sweden.

Table S3 Relative risks of acute myocardial infarction within 14 days after the drug was dispensed, selected by BOLASSO approach in both countries.

Table S4 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed, selected by BOLASSO approach in both countries. AMI diagnosed in hospital only.

Table S5 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed. Univariable results for drugs selected by BOLASSO approach in both the countries. Sub-group analyses according to age in Norway

Table S6 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed. Univariable results for drugs selected by BOLASSO approach in both the countries. Sub-group analyses according to age in Sweden

Supplementary file

Table S1. Relative risks of acute myocardial infarction within 7 days after the drug was dispensed^a. Univariable and BOLASSO results for drugs selected by BOLASSO approach in Norway^b				
ATC ^d	Drug Name	Case window (N exposed) /Control window (N exposed)	Univariable	BOLASSO ^c
			RR (95% CI)	RR (95% CI)
A02BA02	Ranitidine	239 / 143	1.67 (1.36 to 2.06)	1.76 (1.37 to 2.26)
A02BC01	Omeprazole	238 / 213	1.12 (0.93 to 1.34)	1.17 (0.94 to 1.45)
A02BC02	Pantoprazole	662 / 590	1.12 (1.00 to 1.25)	1.14 (1.00 to 1.31)
A02BC05	Esomeprazole	725 / 588	1.23 (1.11 to 1.37)	1.29 (1.13 to 1.48)
A03FA01	Metoclopramide	335 / 220	1.52 (1.38 to 1.81)	1.40 (1.12 to 1.75)
A10BA02	Metformin	693 / 695	0.99 (0.90 to 1.11)	0.95 (0.83 to 1.09)
A10BB12	Glimepiride	341 / 349	0.98 (0.84 to 1.13)	0.91 (0.76 to 1.09)
A10BH01	Sitagliptin	35 / 18	1.94 (1.10 to 3.43)	1.98 (0.99 to 3.98)
A12CC30	Magnesium	39 / 24	1.63 (0.98 to 2.70)	2.09 (0.94 to 4.62)
B01AA03	Warfarin	489 / 493	0.99 (0.88 to 1.12)	0.95 (0.83 to 1.09)
B01AB05	Enoxaparin	78 / 43	1.81 (1.25 to 2.63)	1.85 (1.14 to 3.00)
B01AC04	Clopidogrel	391 / 251	1.56 (1.33 to 1.83)	1.44 (1.19 to 1.76)
B01AC06	Acetylsalicylic acid	3141 / 2803	1.12 (1.06 to 1.18)	1.09 (1.02 to 1.17)
B01AC24	Ticagrelor	27 / 6	4.50 (1.86 to 10.9)	3.12 (1.27 to 7.67)
B03BA03	Hydroxocobalamin	49 / 63	0.78 (0.54 to 1.13)	0.66 (0.43 to 1.02)
C01DA02	Glycerol trinitrate	1758 / 864	2.03 (1.88 to 2.21)	2.15 (1.96 to 2.36)
C01DA14	Isosorbide mononitrate	1072 / 955	1.12 (1.03 to 1.22)	1.00 (0.89 to 1.12)
C03CA01	Furosemide	1317 / 1201	1.10 (1.01 to 1.19)	1.05 (0.95 to 1.17)
C03DA01	Spirolactone	258 / 219	1.18 (0.98 to 1.41)	1.17 (0.92 to 1.48)
C05AA01	Hydrocortisone	3 / 12	0.25 (0.07 to 0.89)	0.21 (0.05 to 0.83)
C07AB02	Metoprolol	2579 / 2289	1.13 (1.07 to 1.19)	1.11 (1.02 to 1.20)
C07AB03	Atenolol	252 / 285	0.88 (0.75 to 1.05)	0.79 (0.65 to 0.96)
C08CA01	Amlodipine	706 / 718	0.98 (0.88 to 1.09)	0.96 (0.85 to 1.09)
C08CA02	Felodipine	112 / 93	1.20 (0.91 to 1.59)	1.34 (0.96 to 1.87)
C08CA05	Nifedipine	199 / 226	0.88 (0.73 to 1.07)	0.78 (0.62 to 0.97)
C09AA05	Ramipril	709 / 683	1.04 (0.93 to 1.15)	0.94 (0.81 to 1.08)

Supplementary file

C09BA02	Enalapril and diuretics	81 / 101	0.80 (0.60 to 1.07)	0.75 (0.53 to 1.05)
C09CA01	Losartan	292 / 310	0.94 (0.80 to 1.11)	0.89 (0.73 to 1.08)
C09CA06	Candesartan	360 / 387	0.93 (0.81 to 1.07)	0.92 (0.77 to 1.09)
C09DA07	Telmisartan and diuretics	17 / 7	2.43 (1.01 to 5.86)	2.26 (0.85 to 6.05)
C10AA01	Simvastatin	1806 / 1748	1.03 (0.97 to 1.10)	0.90 (0.82 to 0.98)
C10AA03	Pravastatin	143 / 184	0.78 (0.62 to 0.97)	0.67 (0.52 to 0.88)
C10AA05	Atorvastatin	608 / 580	1.05 (0.94 to 1.17)	0.85 (0.74 to 0.98)
D07AC01	Betamethasone	76 / 50	1.52 (1.06 to 2.17)	1.31 (0.88 to 1.94)
G04BD11	Fesoterodine	31 / 47	0.66 (0.42 to 1.04)	0.53 (0.27 to 1.04)
H02AB02	Dexamethasone	19 / 8	2.38 (1.04 to 5.43)	2.04 (0.77 to 5.35)
H02AB06	Prednisolone	963 / 823	1.17 (1.07 to 1.28)	1.05 (0.94 to 1.17)
H03AA01	Levothyroxine sodium	629 / 648	0.97 (0.87 to 1.09)	0.92 (0.80 to 1.06)
J01AA02	Doxycycline	324 / 213	1.52 (1.28 to 1.81)	1.51 (1.25 to 1.83)
J01CA04	Amoxicillin	327 / 168	1.95 (1.62 to 2.34)	2.09 (1.69 to 2.58)
J01CA08	Pivmecillinam	309 / 211	1.46 (1.23 to 1.74)	1.45 (1.19 to 1.78)
J01CE02	Phenoxymethylpenicillin	423 / 277	1.53 (1.31 to 1.77)	1.51 (1.29 to 1.77)
J01EA01	Trimethoprim	149 / 114	1.31 (1.02 to 1.67)	1.38 (1.03 to 1.84)
J01FA01	Erythromycin	156 / 89	1.75 (1.35 to 2.27)	1.66 (1.22 to 2.24)
J01FA09	Clarithromycin	59 / 30	1.97(1.27 to 3.05)	1.59 (1.00 to 2.53)
J01FF01	Clindamycin	72 / 49	1.47 (1.02 to 2.11)	1.39 (0.91 to 2.12)
J01MA02	Ciprofloxacin	194 / 134	1.45 (1.16 to 1.80)	1.43 (1.10 to 1.86)
J01XE01	Nitrofurantoin	105 / 66	1.59 (1.17 to 2.16)	1.62 (1.12 to 2.33)
L03AA13	pegfigrastim	16 / 8	2.00 (0.86 to 4.67)	2.41 (0.75 to 7.73)
L04AB01	Etanercept	15 / 22	0.68 (0.35 to 1.31)	0.54(0.24 to 1.21)
M01AB05	Diclofenac	504 / 387	1.30 (1.14 to 1.49)	1.26(1.07 to 1.47)
M04AA01	Allopurinol	351 / 394	0.89 (0.77 to 1.03)	0.85 (0.70 to 1.04)
N02AA01	Morphine	137 / 67	2.04 (1.53 to 2.74)	1.84 (1.21 to 2.79)
N02AA05	Oxycodone	252 / 191	1.32 (1.09 to 1.59)	1.40 (1.07 to 1.84)
N02AA59	Codeine, combinations	1386 / 1202	1.15 (1.07 to 1.25)	1.14 (1.03 to 1.25)
N02AG01	Morphine and antispasmodics	28 / 2	14.0 (3.34 to 58.8)	6.66 (2.31 to 19.3)
N02AX02	Tramadol	512 / 431	1.19 (1.05 to 1.35)	1.24 (1.05 to 1.45)

Supplementary file

N02BE01	Paracetamol	1412 / 1290	1.09 (1.01 to 1.18)	1.02 (0.93 to 1.12)
N03AE01	Clonazepam	51 / 69	0.74 (0.51 to 1.06)	0.60 (0.36 to 1.01)
N03AX16	Pregabalin	112 / 128	0.88 (0.68 to 1.13)	0.69 (0.48 to 0.98)
N05AD01	Haloperidol	55 / 35	1.57 (1.03 to 2.40)	1.71 (0.88 to 3.31)
N05BA01	Diazepam	664 / 575	1.15 (1.03 to 1.29)	1.06 (0.93 to 1.22)
N05BA04	Oxazepam	828 / 757	1.09 (0.99 to 1.21)	1.04 (0.92 to 1.17)
N05CF01	Zopiclone	1618 / 1460	1.11 (1.03 to 1.19)	1.06 (0.97 to 1.17)
N05CF02	Zolpidem	175 / 191	0.92 (0.75 to 1.12)	0.85 (0.67 to 1.07)
N06AB04	Citalopram	170 / 182	0.93 (0.76 to 1.15)	0.85 (0.66 to 1.11)
N06AB06	Sertraline	90 / 98	0.92 (0.69 to 1.22)	0.78 (0.53 to 1.13)
N06AB10	Escitalopram	333 / 352	0.95 (0.81 to 1.10)	0.89 (0.73 to 1.09)
N06AX16	Venlafaxine	91 / 103	0.88 (0.67 to 1.17)	0.79 (0.54 to 1.15)
P01AB01	Metronidazole	51 / 51	1.00 (0.68 to 1.47)	0.60 (0.38 to 0.94)
R01AD09	Mometasone	83 / 100	0.83 (0.62 to 1.11)	0.74 (0.54 to 1.03)
R03AC02	Salbutamol	653 / 532	1.23 (1.09 to 1.37)	1.16 (1.00 to 1.34)
R03AC03	Terbutaline	92 / 77	1.19 (0.88 to 1.62)	1.24 (0.89 to 1.73)
R03AK06	Salmeterol and other anti-asthmatics	250 / 278	0.90 (0.76 to 1.07)	0.83 (0.69 to 1.00)
R03BA02	Budesonide	40 / 56	0.71 (0.48 to 1.07)	0.71 (0.44 to 1.14)
R03BA05	Fluticasone	34 / 42	0.81 (0.52 to 1.27)	0.66 (0.39 to 1.12)
R05CB01	Acetylcysteine	519 / 394	1.32 (1.16 to 1.50)	1.11 (0.96 to 1.30)
R05DA01	Ethylmorphine	288 / 199	1.45 (1.21 to 1.73)	1.35 (1.10 to 1.66)
R05FA02	Opium derivatives and expectorants	71 / 35	2.03 (1.35 to 3.04)	1.59 (1.00 to 2.54)
S01EA05	Brimonidine	37 / 10	3.70 (1.84 to 7.44)	3.21 (1.51 to 6.84)
S01ED02	Betaxolol	7 / 18	0.39 (0.16 to 0.93)	0.46 (0.18 to 1.18)

^a Case-crossover analysis, case period (1 to 7 days) and control period (15 to 21 days) before the index-date for the diagnosis of AMI.

^b Data from the Norwegian Prescription Database, 2004-2014

^c In BOLASSO, the effect of each selected drugs is controlled for the effect of other selected drugs.

^d Classified according to Anatomical Therapeutic Chemical (ATC), 5th level

Supplementary file

Table S2. Relative risks of acute myocardial infarction within 7 days after the drug was dispensed^a. Univariable and BOLASSO results for drugs selected by BOLASSO in Sweden^b

ATC ^d	Drug Name	Case window (N exposed) /Control window (N exposed)	Univariable	BOLASSO ^c
			RR (95% CI)	RR (95% CI)
A02AD01	Ordinary Salt Combinations	58 / 34	1.71 (1.12 to 2.60)	1.44 (0.91 to 2.28)
A02BC01	Omeprazole	8870 / 8261	1.07 (1.04 to 1.11)	1.12 (1.07 to 1.18)
A02BC05	Esomeprazole	871 / 802	1.09 (0.99 to 1.20)	1.09 (0.96 to 1.25)
A02BX02	Sucralfate	43 / 22	1.95 (1.17 to 3.27)	2.53 (1.21 to 5.29)
A03AB02	Glycopyrronium Bromide	52 / 8	6.50 (3.09 to 13.7)	4.19 (1.77 to 9.89)
A03AD01	Papaverine	96 / 68	1.41 (1.03 to 1.93)	1.54 (1.05 to 2.25)
A03FA01	Metoclopramide	709 / 503	1.41 (1.26 to 1.58)	1.49 (1.28 to 1.73)
A06AB08	Sodium picosulfate	632 / 621	1.02(0.91 to 1.14)	0.87 (0.77 to 0.99)
A06AG10	Docusate sodium, incl. combinations	53 / 22	2.41 (1.47 to 3.96)	1.79 (1.03 to 3.10)
A07AA02	Nystatin	372 / 248	1.50 (1.28 to 1.76)	1.48 (1.23 to 1.78)
A10AD05	Insulin Aspart	889 / 907	0.98 (0.89 to 1.08)	0.95 (0.86 to 1.04)
A10AE04	Insulin Glargine	389 / 462	0.84 (0.74 to 0.96)	0.85 (0.72 to 1.00)
A10BA02	Metformin	2659 / 2896	0.92 (0.87 to 0.97)	0.86 (0.79 to 0.94)
A10BB01	Glibenclamide	1002 / 1054	0.95 (0.87 to 1.04)	0.91 (0.79 to 1.04)
A11CC03	Alfacalcidol	458 / 484	0.95 (0.83 to 1.08)	0.86 (0.70 to 1.06)
A11EX	Vitamin B-Complex, other combinations	299 / 334	0.90 (0.77 to 1.05)	0.87 (0.73 to 1.05)
A11HA03	Tocopherol	31 / 46	0.67 (0.43 to 1.06)	0.58 (0.33 to 1.03)
A12BA01	Potassium Chloride	2035 / 1914	1.06 (0.99 to 1.13)	1.10 (0.98 to 1.23)
B01AB05	Enoxaparin	126 / 93	1.35 (1.04 to 1.77)	1.34 (0.98 to 1.83)
B01AC04	Clopidogrel	1290 / 852	1.51 (1.39 to 1.65)	1.78 (1.57 to 2.01)
B01AC06	Acetylsalicylic acid	15489 / 15240	1.02 (0.99 to 1.04)	0.99 (0.95 to 1.03)
B01AC07	Dipyridamole	288 / 343	0.84 (0.72 to 0.98)	0.87 (0.72 to 1.03)
B01AC24	Ticagrelor	96 / 14	6.86 (3.91 to 12.0)	5.14 (2.85 to 9.26)
B01AF01	Rivaroxaban	31 / 16	1.94 (1.06 to 3.54)	2.31 (0.96 to 5.55)
B03AA07	Ferrous sulfate	2429 / 2320	1.05 (0.99 to 1.11)	1.07 (0.97 to 1.19)
B03AC	Iron, parenteral preparations	48 / 29	1.66 (1.04 to 2.62)	1.55 (0.93 to 2.57)

Supplementary file

B03BA01	Cyanocobalamin	7517 / 7514	1.00 (0.97 to 1.03)	0.99 (0.93 to 1.06)
B03BA03	Hydroxocobalamin	125 / 155	0.81 (0.64 to 1.02)	0.79 (0.61 to 1.01)
B03BB01	Folic Acid	4398 / 4474	0.98 (0.94 to 1.02)	0.90 (0.82 to 0.98)
B03XA01	Erythropoietin	109 / 128	0.85 (0.66 to 1.10)	0.75 (0.56 to 1.00)
C01AA05	Digoxin	2425 / 2387	1.02 (0.96 to 1.07)	0.94 (0.85 to 1.04)
C01DA02	Glycerol Trinitrate	5020 / 2949	1.70 (1.63 to 1.78)	1.84 (1.74 to 1.94)
C03AA01	Bendroflumethiazide	1376 / 1398	0.98 (0.91 to 1.06)	0.95 (0.86 to 1.05)
C03AB01	Bendroflumethiazide and potassium	68 / 100	0.68 (0.50 to 0.93)	0.56 (0.38 to 0.83)
C03CA01	Furosemide	14307 / 13807	1.04 (1.01 to 1.06)	1.04 (0.99 to 1.09)
C03DA01	Spironolactone	2716 / 2674	1.02 (0.96 to 1.07)	0.94 (0.86 to 1.03)
C03EA01	Hydrochlorothiazide and potassium-sparing agents	974 / 1082	0.90 (0.83 to 0.98)	0.80 (0.71 to 0.91)
C07AB02	Metoprolol	8861 / 8437	1.05 (1.02 to 1.08)	1.05 (1.00 to 1.11)
C07AB03	Atenolol	2836 / 2823	1.00 (0.95 to 1.06)	1.01 (0.93 to 1.09)
C07AB07	Bisoprolol	2727 / 2562	1.06 (1.01 to 1.12)	1.06 (0.97 to 1.15)
C08CA01	Amlodipine	2512 / 2544	0.99 (0.93 to 1.04)	0.92 (0.85 to 1.00)
C08CA02	Felodipine	3529 / 3617	0.98 (0.93 to 1.02)	0.91 (0.85 to 0.98)
C09AA02	Enalapril	5783 / 5716	1.01 (0.98 to 1.05)	0.98 (0.92 to 1.04)
C09AA05	Ramipril	1870 / 1855	1.01 (0.95 to 1.07)	0.92 (0.83 to 1.02)
C09CA01	Losartan	1728 / 1738	0.99 (0.93 to 1.06)	0.95 (0.86 to 1.05)
C09CA04	Irbesartan	233 / 263	0.89 (0.74 to 1.06)	0.78 (0.61 to 1.01)
C09CA06	Candesartan	1363 / 1448	0.94 (0.87 to 1.01)	0.88 (0.79 to 0.98)
C10AA01	Simvastatin	5611 / 5672	0.99 (0.95 to 1.03)	0.94 (0.88 to 0.99)
D07AB02	Hydrocortisone butyrate	143 / 199	0.72 (0.58 to 0.89)	0.78 (0.61 to 0.98)
G03CA03	Estradiol	483 / 545	0.89 (0.78 to 1.00)	0.86 (0.75 to 0.99)
G03XC01	Raloxifene	28 / 18	1.56 (0.86 to 2.81)	2.36 (0.86 to 6.48)
G04BD07	Tolterodine	582 / 629	0.93 (0.83 to 1.04)	0.84 (0.69 to 1.03)
G04BE03	Sildenafil	135 / 180	0.75 (0.60 to 0.94)	0.75 (0.58 to 0.97)
G04BE08	Tadalafil	97 / 132	0.73 (0.57 to 0.96)	0.73 (0.54 to 0.98)
G04CA01	Alfuzosin	824 / 855	0.96 (0.86 to 1.06)	0.87 (0.76 to 1.00)
G04CB01	Finasteride	375 / 494	0.76 (0.66 to 0.87)	0.74 (0.64 to 0.86)
H02AB01	Betamethasone	802 / 568	1.41 (1.27 to 1.57)	1.21 (1.06 to 1.37)

Supplementary file

H02AB06	Prednisolone	3692 / 3486	1.06 (1.01 to 1.11)	1.05 (0.97 to 1.13)
H03AA01	Levothyroxine Sodium	4843 / 4863	0.99 (0.96 to 1.04)	0.93 (0.86 to 1.01)
J01AA02	Doxycycline	1095 / 591	1.85 (1.68 to 2.05)	1.76 (1.58 to 1.96)
J01CA04	Amoxicillin	575 / 353	1.63 (1.43 to 1.86)	1.44 (1.24 to 1.66)
J01CA08	Pivmecillinam	535 / 422	1.27 (1.12 to 1.44)	1.21 (1.05 to 1.41)
J01CE02	Phenoxymethylpenicillin	847 / 595	1.42 (1.28 to 1.58)	1.34 (1.20 to 1.50)
J01CF05	Flucloxacillin	872 / 943	0.92 (0.84 to 1.01)	0.89 (0.80 to 0.99)
J01DB05	Cefadroxil	226 / 157	1.44 (1.17 to 1.76)	1.39 (1.09 to 1.78)
J01EA01	Trimethoprim	402 / 281	1.43 (1.23 to 1.67)	1.60 (1.33 to 1.92)
J01EE01	Sulfamethoxazole and trimethoprim	175 / 119	1.47 (1.17 to 1.86)	1.49 (1.15 to 1.93)
J01FA01	Erythromycin	90 / 36	2.50 (1.70 to 3.68)	2.14 (1.39 to 3.30)
J01MA02	Ciprofloxacin	830 / 630	1.32 (1.19 to 1.46)	1.35 (1.19 to 1.52)
J01XE01	Nitrofurantoin	365 / 249	1.47 (1.25 to 1.72)	1.56 (1.29 to 1.89)
J02AC01	Fluconazole	232 / 164	1.41 (1.16 to 1.73)	1.34 (1.06 to 1.69)
M01AB05	Diclofenac	1180 / 1001	1.18 (1.08 to 1.28)	1.15 (1.04 to 1.28)
M01AH05	Etoricoxib	101 / 118	0.86 (0.66 to 1.12)	0.77 (0.57 to 1.04)
M03BA02	Carisoprodol	13 / 29	0.45 (0.23 to 0.86)	0.52 (0.26 to 1.03)
M04AA01	Allopurinol	1897 / 1952	0.97 (0.91 to 1.04)	0.93 (0.83 to 1.03)
M05BA04	Alendronic Acid	1172 / 1204	0.97 (0.90 to 1.05)	0.92 (0.80 to 1.05)
N02AA01	Morphine	2195 / 1515	1.45 (1.36 to 1.55)	1.69 (1.52 to 1.89)
N02AA05	Oxycodone	2659 / 2337	1.14 (1.08 to 1.20)	1.21 (1.10 to 1.34)
N02AA59	Codeine, combinations	1526 / 1391	1.10 (1.02 to 1.18)	1.09 (1.00 to 1.20)
N02AB03	Fentanyl	670 / 514	1.30 (1.16 to 1.46)	1.28 (1.11 to 1.48)
N02AC04	Dextropropoxyphene	1056 / 1050	1.01 (0.92 to 1.10)	0.93 (0.82 to 1.05)
N02AG01	Morphine and antispasmodics	256 / 42	6.10 (4.40 to 8.45)	5.92 (4.09 to 8.57)
N02AG02	Ketobemidone and antispasmodics	50 / 17	2.94 (1.70 to 5.10)	2.28 (1.18 to 4.42)
N02BE01	Paracetamol	14481 / 14036	1.03 (1.01 to 1.06)	1.01 (0.97 to 1.05)
N04BA02	Levodopa and decarboxylase Inhibitor	1243 / 1254	0.99 (0.92 to 1.07)	0.89 (0.75 to 1.06)
N05AX08	Risperidone	1842 / 1795	1.03 (0.96 to 1.10)	1.14 (0.97 to 1.35)
N05BA01	Diazepam	1165 / 957	1.22 (1.12 to 1.33)	1.12 (0.99 to 1.26)
N05CD03	Flunitrazepam	556 / 575	0.97 (0.86 to 1.09)	0.84 (0.70 to 1.02)

Supplementary file

N05CD08	Midazolam	47 / 8	5.88 (2.78 to 12.4)	2.31(1.14 to4.65)
N05CF01	Zopiclone	5999 / 6024	1.00 (0.96 to 1.03)	0.96 (0.90 to1.02)
N05CF02	Zolpidem	2555 / 2564	1.00 (0.94 to 1.05)	0.97 (0.89 to1.05)
N06AB04	Citalopram	5548 / 5513	1.01 (0.97 to 1.04)	0.97 (0.90 to1.05)
N06AB06	Sertraline	1358 / 1360	1.00 (0.93 to 1.08)	0.90 (0.78 to1.04)
N06AX11	Mirtazapine	2809 / 2754	1.02 (0.97 to1.08)	1.06 (0.95 to1.18)
P01AB01	Metronidazole	169 / 185	0.91 (0.74 to1.13)	0.73 (0.57 to0.93)
R01AD09	Mometasone	326 / 338	0.96 (0.83 to1.12)	0.87 (0.73 to1.03)
R03AC02	Salbutamol	618 / 526	1.17 (1.05 to1.32)	1.12 (0.98 to1.28)
R03AC03	Terbutali	968 / 787	1.23 (1.12 to1.35)	1.16 (1.04 to1.30)
R03AC12	Salmeterol	73 / 56	1.30 (0.92 to1.85)	1.35 (0.92 to1.98)
R03AK07	Formoterol and budesonide	941 / 810	1.16 (1.06 to1.28)	1.12 (1.00 to1.25)
R03AL02	Salbutamol and ipratropium bromide	387 / 322	1.20 (1.04 to1.39)	1.13 (0.95 to1.34)
R03BB04	Tiotropium Bromide	857 / 823	1.04 (0.95 to1.15)	0.94 (0.84 to1.06)
R03DA02	Choline theophyllinate	105 / 59	1.78 (1.29 to2.45)	1.69 (1.12 to2.55)
R05CB01	Acetylcysteine	1677 / 1375	1.22 (1.14 to1.31)	1.14 (1.05 to1.24)
R05CB10	Mucolytics	733 / 422	1.74 (1.54 to1.96)	1.53 (1.34 to1.75)
R05DA20	Opium Alkaloids and derivatives	62 / 23	2.70 (1.67 to4.35)	2.37 (1.35 to4.16)
R05FA02	Opium Derivatives and expectorants	828 / 438	1.89 (1.68 to2.12)	1.73 (1.52 to1.97)
S01BA02	Hydrocortisone	17 / 40	0.43 (0.24 to0.75)	0.53 (0.28 to1.02)
S01ED51	Timolol, Combinations	508 / 481	1.06 (0.93 to1.20)	1.10 (0.95 to1.27)
V03AE02	Sevelamer	95 / 77	1.23 (0.91 to1.67)	1.39 (0.99 to1.97)
Y92BA00	Teststickor För Blodglukos	1634 / 1667	0.98 (0.92 to1.05)	0.95 (0.87 to1.04)
Y92EA00	Lancetter Till Blodprovstagare	325 / 286	1.14 (0.97 to1.33)	1.18 (0.98 to1.43)

^a Case-crossover analysis, case period (1 to 7 days) and control period (15 to 21 days) before the index-date for the diagnosis of AMI.

^b Data from the Swedish Prescribed Drug Register, 2005 to 2014

^c In BOLASSO, the effect of each selected drugs is controlled for the effect of other selected drugs.

^d Classified according to Anatomical Therapeutic Chemical (ATC), 5th level

Supplementary file

Table S3 Relative risks of acute myocardial infarction within 14 days after the drug was dispensed^a, selected by BOLASSO^b approach in both countries.

		SWEDEN ^c			NORWAY ^d			TOTAL ^e
ATC ^f	Drug Names	Case window (exposed); N	Control window (exposed); N	RR (95% CI)	Case window (exposed); N	Control window (exposed); N	RR (95% CI)	Combined Estimate RR (95% CI)
A02BC01	Omeprazole	16268	14553	1.19 (1.14 -1.24)	411	369	1.12 (0.93-1.34)	1.18 (1.13-1.23)
A02BC05	Esomeprazole	1561	1364	1.22 (1.09-1.37)	1261	1025	1.29 (1.16-1.43)	1.26 (1.16-1.36)
A03FA01	Metoclopramide	1181	790	1.48 (1.31-1.68)	529	307	1.60 (1.32-1.93)	1.52 (1.37-1.68)
A07AA02	Nystatin	633	362	1.55 (1.35 -1.79)	113	79	1.39 (0.99-1.96)	1.53 (1.34 -1.74)
A10BA02	Metformin	5076	5268	0.87 (0.82-0.93)	1297	1301	0.94 (0.84-1.04)	0.89 (0.84 -0.94)
A12AX	Calcium	6480	6440	0.97 (0.91-1.03)	953	971	0.90 (0.78-1.03)	0.96 (0.91-1.01)
B01AA03	Warfarin	2285	2357	0.90 (0.85-0.96)	920	940	0.91 (0.81-1.01)	0.90 (0.86-0.95)
B01AB05	Enoxaparin	219	153	1.44 (1.11-1.87)	134	88	1.65 (1.15-2.37)	1.51 (1.22-1.86)
B01AC04	Clopidogrel	2157	1565	1.58 (1.44-1.74)	578	395	1.53 (1.29-1.80)	1.57 (1.44-1.70)
B01AC06	Acetylsalicylic Acid	29062	27782	0.98 (0.95-1.01)	5678	5178	1.03 (0.98-1.09)	0.99 (0.97-1.02)
B01AC24	Ticagrelor	108	19	4.20 (2.42-7.30)	39	7	5.21 (2.18-12.5)	4.47 (2.80-7.12)
C01DA02	Glyceral Trinitrate	8094	4635	1.87 (1.79-1.96)	2668	1278	2.29 (2.11-2.48)	1.96 (1.89-2.04)
C01DA14	Isosorbide Mononitrate	10659	9412	1.08 (1.02-1.13)	1935	1659	1.06 (0.96-1.17)	1.08 (1.03-1.13)
C03AB01	Bendroflumethiazide & Potassium	141	186	0.68 (0.51-0.91)	229	166	1.48 (1.17-1.88)	1.08 (0.90- 1.30)
C03CA01	Furosemide	26628	24790	1.08 (1.03-1.12)	2395	2226	1.01 (0.93 -1.11)	1.07 (1.03 -1.11)
C03DA01	Spironolactone	5025	4805	0.96 (0.89-1.03)	418	419	0.87 (0.72-1.05)	0.95 (0.89-1.02)
C07AB02	Metoprolol	16589	15251	1.08 (1.04-1.13)	4635	4118	1.09 (1.02-1.16)	1.08 (1.05-1.12)
C07AB07	Bisoprolol	5082	4588	1.09 (1.01-1.16)	440	388	1.15 (0.95-1.39)	1.10 (1.03-1.17)
C08CA01	Amlodipine	4814	4774	0.93 (0.88-0.99)	1308	1345	0.88 (0.80-0.97)	0.92 (0.87-0.96)
C09AA03	Isinopril	384	399	0.85 (0.68-1.06)	371	317	1.18 (0.98-1.42)	1.03 (0.89-1.19)
C09CA03	Valsartan	347	376	0.76 (0.62-0.94)	219	184	1.17 (0.93-1.47)	0.92 (0.79-1.08)
C09CA06	Candesartan	2639	2618	0.96 (0.89-1.04)	693	669	1.15 (0.98-1.37)	0.99 (0.92-1.06)
C10AA01	Simvastatin	10637	10262	0.94 (0.90-0.98)	3322	3210	0.92 (0.86-0.98)	0.93 (0.90-0.97)
C10AA03	Pravastatin	311	364	0.74 (0.60-0.91)	280	296	0.77 (0.62-0.96)	0.75 (0.65-0.88)

Supplementary file

C10AA05	Atorvastatin	1784	1639	0.97 (0.88-1.06)	1130	1003	0.94 (0.84-1.05)	0.96 (0.89-1.03)
G03FA01	Norethisterone And Estrogen	87	120	0.68 (0.48-0.96)	51	70	0.73 (0.50-1.07)	0.70 (0.54-0.91)
G04BD07	Tolterodine	1107	1165	0.77 (0.66-0.91)	186	205	0.78 (0.58-1.04)	0.77 (0.67-0.89)
H02AB06	Prednisolone	6819	6259	1.09 (1.02-1.16)	1690	1419	1.14 (1.04-1.25)	1.11 (1.05-1.17)
H03AA01	Levothyroxine Sodium	9399	9173	0.96 (0.90-1.03)	1212	1296	0.84 (0.75-0.94)	0.93 (0.88-0.98)
J01AA02	Doxycycline	1709	1019	1.54 (1.42-1.68)	524	277	1.72 (1.48-2.01)	1.58 (1.47-1.70)
J01CA04	Amoxicillin	937	599	1.48 (1.32-1.66)	511	296	1.59 (1.34-1.89)	1.51 (1.38-1.66)
J01CA08	Pivmecillinam	934	695	1.32 (1.19-1.48)	507	409	1.26 (1.09-1.47)	1.30 (1.19-1.42)
J01CE02	Phenoxymethylpenicillin	1332	985	1.26 (1.15-1.38)	675	452	1.46 (1.28-1.66)	1.32 (1.23-1.43)
J01FA01	Erythromycin	130	78	1.68 (1.21-2.34)	232	142	1.52 (1.21-1.91)	1.57 (1.30-1.89)
J01FF01	Clindamycin	593	516	1.12 (0.97-1.29)	123	72	1.61 (1.15-2.26)	1.18 (1.04-1.35)
J01MA02	Ciprofloxacin	1454	970	1.46 (1.33-1.60)	315	238	1.32 (1.09-1.61)	1.43 (1.32-1.56)
J01XE01	Nitrofurantoin	610	405	1.64 (1.41-1.90)	171	132	1.40 (1.06-1.86)	1.58 (1.39-1.81)
L01BC06	Capecitabine	51	21	2.02 (0.92-4.44)	19	4	2.74 (0.92-8.13)	2.24 (1.19-4.24)
M01AB05	Diclofenac	2158	1934	1.08 (1.00-1.16)	848	676	1.22 (1.09-1.36)	1.12 (1.06-1.19)
M01AX05	Glucosamine	504	542	0.87 (0.74-1.02)	98	144	0.64 (0.47-0.87)	0.82 (0.71-0.94)
N02AA01	Morphine	3629	2468	2.02 (1.83-2.24)	213	119	1.55 (1.10-2.18)	1.98 (1.80-2.18)
N02AA05	Oxycodone	4805	3879	1.41 (1.30-1.53)	471	342	1.69 (1.34-2.13)	1.44 (1.33-1.55)
N02AA59	Codeine, Combinations	2749	2484	1.12 (1.03-1.21)	2450	2102	1.18 (1.09-1.28)	1.15 (1.09-1.22)
N02AB03	Fentanyl	1190	897	1.41 (1.24-1.59)	220	151	1.49 (1.09-2.05)	1.42 (1.27-1.60)
N02AG01	Morphine and antispasmodics	314	57	5.86 (4.15-8.27)	32	0	18.74(8.71-40.34)	7.13 (5.20-9.76)
N02AG02	Ketobemidone and antispasmodics	74	34	2.45 (1.42-4.21)	30	16	2.40 (0.87-6.61)	2.44 (1.51-3.94)
N02AX02	Tramadol	3963	3748	1.06 (0.99-1.13)	905	745	1.22 (1.07-1.38)	1.09 (1.03-1.16)
N02BE01	Paracetamol	27229	25369	1.03 (1.00-1.07)	2585	2308	1.06 (0.98-1.14)	1.04 (1.00-1.07)
N05BA01	Diazepam	2062	1731	1.19 (1.07-1.31)	1182	1049	1.06 (0.96-1.18)	1.12 (1.05-1.21)
N05BA04	Oxazepam	9286	8644	1.09 (1.03-1.15)	1540	1360	1.12 (1.01-1.24)	1.11 (1.03-1.19)
N05CF01	Zopiclone	11300	10828	1.03 (0.97-1.08)	2920	2816	0.97 (0.91-1.04)	1.01 (0.97-1.05)
N06AX11	Mirtazapine	5299	4958	1.19 (1.08-1.30)	339	302	1.20 (0.94-1.53)	1.19 (1.09-1.30)
R01AD09	Mometasone	628	620	0.93 (0.82-1.05)	151	193	0.68 (0.53-0.86)	0.87 (0.78-0.97)
R03AC02	Salbutamol	1121	942	1.19 (1.06-1.33)	1176	987	1.20 (1.07-1.34)	1.20 (1.10-1.29)

Supplementary file

R03AK06	Salmeterol and fluticasone	603	600	0.91 (0.80-1.04)	475	525	0.80 (0.69-0.94)	0.86 (0.78-0.95)
R03BA02	Budesonide	1145	1112	0.90 (0.81-0.99)	86	93	0.76 (0.54-1.06)	0.89 (0.81-0.98)
R03BB04	Tiotropium Bromide	1627	1661	0.89 (0.81-0.98)	394	417	0.87 (0.74-1.01)	0.88 (0.82-0.96)
S03CA04	Hydrocortisone & antiinfectives	456	498	0.90 (0.78-1.02)	58	73	0.75 (0.52-1.08)	0.88 (0.78-1.00)

^a Case-crossover analysis, case period (1 to 14 days) and control period (29 to 42 days) before the index date for the diagnosis of AMI. ^b In BOLASSO, the effect of each selected drugs is controlled for the effect of other selected drugs.

^c Data from the Swedish Prescribed Drug Register , 2005 to 2014

^d Data from the Norwegian Prescription Database, 2004 to 2014

^e Combined estimates of Norwegian and Swedish data calculated using fixed-effect

^f Classified according to Anatomical Therapeutic Chemical (ATC), 5th level

Supplementary file

Table S4 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed^a, selected by BOLASSO^b approach in both countries. AMI diagnosed in hospital only.

		SWEDEN ^c			NORWAY ^d			TOTAL ^e
ATC ^f	Drug Names	Case window (exposed); N	Control window (exposed); N	RR (95% CI)	Case window (exposed); N	Control window (exposed); N	RR (95% CI)	Combined Estimate RR (95% CI)
	<i>Narcotic analgesics</i>							
R05FA02	Opium derivatives and expectorants	695	391	1.60 (1.39-1.85)	61	29	1.66 (1.00-2.75)	1.60 (1.40- 1.84)
N02AA05	Oxycodone	1952	1735	1.17 (1.04-1.31)	195	146	1.45 (1.09-1.94)	1.21 (1.08- 1.34)
N02AA59	Codeine, combinations	1234	1143	1.06 (0.96-1.17)	1078	991	1.07 (0.97-1.18)	1.07 (0.99-1.14)
	<i>Antibiotics</i>							
J01FA01	Erythromycin	82	30	2.37 (1.47-3.84)	130	71	1.77 (1.27-2.48)	1.95 (1.48- 2.56)
J01XE01	Nitrofurantoin	316	189	1.74 (1.42-2.13)	92	54	1.71 (1.14-2.58)	1.73 (1.45- 2.08)
J01EA01	Trimethoprim	318	202	1.79 (1.45-2.20)	119	90	1.42 (1.03-1.95)	1.67 (1.40- 1.99)
J01AA02	Doxycycline	916	526	1.63 (1.45-1.84)	264	174	1.52 (1.23-1.89)	1.60 (1.45- 1.78)
J01CA04	Amoxicillin	456	295	1.38 (1.17-1.62)	264	135	2.12 (1.69-2.67)	1.59 (1.40-1.82)
J01MA02	Ciprofloxacin	677	504	1.38 (1.20-1.58)	156	103	1.55 (1.16-2.07)	1.41 (1.25- 1.60)
J01EE01	Sulfamethoxazole & trimethoprim	142	100	1.39 (1.06-1.84)	70	43	1.46 (0.96-2.23)	1.41 (1.12- 1.78)
J01CE02	Phenoxymethylpenicillin	702	514	1.30 (1.14-1.47)	337	226	1.45 (1.21-1.75)	1.35 (1.21- 1.50)
J01CA08	Pivmecillinam	442	351	1.23 (1.05-1.45)	256	173	1.50 (1.21-1.85)	1.32 (1.16- 1.50)
	<i>Antithrombotic agents</i>							
B01AC24	Ticagrelor	94	13	5.22 (2.83-9.64)	26	6	3.11 (1.26-7.70)	4.44 (2.67- 7.37)
B01AC04	Clopidogrel	1126	701	1.82 (1.61-2.06)	319	214	1.40 (1.14-1.72)	1.70 (1.53-1.89)
B01AB05	Enoxaparin	107	72	1.41 (1.00-2.00)	66	29	2.46 (1.35-4.48)	1.62 (1.20-2.19)
B01AC06	Acetylsalicylic acid	11864	11515	1.01 (0.96-1.05)	2694	2396	1.11 (1.02-1.20)	1.03 (0.99-1.07)
	<i>Adrenergics</i>							
R03AC03	Terbutaline	831	667	1.16 (1.03-1.31)	75	58	1.42 (0.96-2.10)	1.18 (1.05-1.32)
R03AC02	Salbutamol	527	449	1.12 (0.97-1.30)	510	426	1.12 (0.95-1.32)	1.12 (1.00- 1.25)
	<i>Protonpump inhibitor</i>							
A02BC01	Omeprazole	6698	6126	1.14 (1.07-1.20)	204	186	1.17 (0.92-1.48)	1.15 (1.08- 1.21)
	<i>Vasodilator</i>							
C01DA02	Glycerol trinitrate	4607	2656	1.88 (1.78-1.99)	1549	729	2.27 (2.05-2.52)	1.96 (1.87-2.06)
	<i>Antiinflammatory drug</i>							
M01AB05	Diclofenac	1033	854	1.19 (1.07-1.33)	434	340	1.19 (1.02-1.40)	1.19 (1.09-1.30)
	<i>Prokinetic/antiemetic drug</i>							

Supplementary file

A03FA01	Metoclopramide	464	348	1.40 (1.16-1.69)	232	153	1.39 (1.06-1.81)	1.40 (1.20-1.63)
	Mucolytics							
R05CB01	Acetylcysteine	1360	1105	1.15 (1.05-1.27)	394	312	1.07 (0.91-1.26)	1.13 (1.04-1.23)
	Glucocorticoid							
H02AB06	Prednisolone	2883	2659	1.06 (0.98-1.15)	804	671	1.08 (0.95-1.23)	1.07 (1.00-1.14)
	Betatoblocker							
C07AB02	Metoprolol	6969	6602	1.03 (0.98-1.09)	2152	1909	1.09 (1.00-1.20)	1.05 (1.00-1.09)
	Nontoxic analgesic							
N02BE01	Paracetamol	10453	10145	1.02 (0.98-1.07)	1165	1059	1.04 (0.93-1.15)	1.02 (0.98-1.06)
	Anxiolytic							
N05BA04	Oxazepam	3331	3250	0.99 (0.92-1.07)	656	597	1.04 (0.91-1.19)	1.00 (0.94-1.07)
	Hypnotics and sedatives							
N05CF01	Zopiclone	4299	4312	0.95 (0.89-1.01)	1302	1187	1.05 (0.95-1.16)	0.98 (0.93-1.03)
N05CF02	Zolpidem	2022	2054	0.94 (0.86-1.02)	147	162	0.82 (0.63-1.07)	0.93 (0.86-1.01)
	Calcium Channel blockers							
C08CA02	Felodipine	2955	2984	0.93 (0.86-1.01)	103	81	1.51 (1.04-2.19)	0.95 (0.88-1.03)
C08CA01	Amlodipine	2090	2119	0.91 (0.84-1.00)	600	620	0.95 (0.83-1.09)	0.92 (0.86-0.99)
	ACE inhibitor							
C09AA05	Ramipril	1439	1407	0.93 (0.84-1.04)	547	540	0.93 (0.80-1.08)	0.93 (0.85-1.02)
	Lipid modifying agent							
C10AA01	Simvastatin	4730	4717	0.95 (0.90-1.01)	1544	1504	0.89 (0.80-0.99)	0.94 (0.89-0.99)
	Antithyroid agent							
H03AA01	Levothyroxine sodium	3530	3597	0.90 (0.83-0.99)	534	556	0.92 (0.80-1.07)	0.91 (0.84-0.98)
	Antidiabetic drug							
A10BA02	Metformin	2178	2362	0.86 (0.78-0.94)	584	588	0.95 (0.82-1.10)	0.89 (0.82-0.96)
	Antidepressant							
N06AB06	Sertraline	928	949	0.85 (0.73-1.00)	72	80	0.71 (0.47-1.09)	0.83 (0.72-0.96)
	Antiprotozoal drug							
P01AB01	Metronidazole	132	141	0.77 (0.58-1.02)	39	43	0.55 (0.32-0.92)	0.72 (0.56-0.92)

^a Case-crossover analysis, case period (1 to 7 days) and control period (15 to 21 days) before the index-date for the diagnosis of AMI.

^b In BOLASSO, the effect of each selected drug is controlled for the effect of other selected drugs. ^c Data from the Swedish Prescribed register, 2005 to 2014

^d Data from the Norwegian Prescribed Database, 2004 to 2014

^e Combined estimates of Norwegian and Swedish data calculated using fixed-effect model

^f Classified according to Anatomical Therapeutic Chemical (ATC), 5th level

Supplementary file

Table S5 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed. Univariable results for drugs selected by BOLASSO approach in both the countries. Sub-group analyses according to age in Norway							
				Norway [‡] < 80 years			Norway [‡] ≥80 years
ATC Code ^s	Drug Names	Case window (exposed); N	Control window (exposed); N	RR (95% CI)	Case window (exposed); N	Control window (exposed); N	RR (95% CI)
	<i>Narcotic analgesics</i>						
N02AG01	Morphine & antispasmodics	NA	NA	NA	28	2	14.0 (3.33-58.77)
N02AA01	Morphine	25	24	1.04 (0.59-1.82)	112	43	2.60 (1.83-3.70)
N02AA05	Oxycodone	135	95	1.42 (1.09-1.85)	117	96	1.22 (0.93-1.60)
N02AA59	Codeine, combinations	759	686	1.11 (1.00-1.23)	627	516	1.22 (1.08-1.37)
R05FA02	Opium derivatives & expectorant	34	22	1.55 (0.90-2.64)	37	13	2.85 (1.51-5.35)
	<i>Non-narcotic analgesic</i>						
N02BE01	Paracetamol	517	489	1.05 (0.93-1.19)	895	801	1.12 (1.01-1.23)
	<i>Anti-inflammatory drugs</i>						
M01AB05	Diclofenac	344	299	1.15 (0.99-1.34)	160	88	1.82 (1.40-2.36)
	<i>Antibiotics</i>						
J01FA01	Erythromycin	95	45	2.11 (1.48-3.01)	61	44	1.39 (0.94-2.04)
J01AA02	Doxycycline	176	131	1.34 (1.07-1.68)	148	82	1.80 (1.38-2.36)
J01CA04	Amoxicillin	158	84	1.88 (1.44-2.45)	169	84	2.01 (1.55-2.61)
J01XE01	Nitrofurantoin	37	19	1.95 (1.12-3.39)	68	47	1.45 (1.00-2.10)
J01EA01	Trimethoprim	48	38	1.26 (0.83-1.93)	101	76	1.33 (0.99-1.79)
J01CE02	Phenoxymethylpenicillin	215	150	1.43 (1.16-1.77)	208	127	1.64 (1.31-2.04)
J01MA02	Ciprofloxacin	86	56	1.54 (1.10-2.15)	108	78	1.38 (1.03-1.85)
J01CA08	Pivmecillinam	101	72	1.40 (1.04-1.90)	208	139	1.50 (1.21-1.85)
	<i>Antiprotozoal drug</i>						
P01AB01	Metronidazole	26	29	0.90 (0.53-1.52)	25	22	1.14 (0.64-2.02)
	<i>Antithrombotic agents</i>						
B01AC24	Ticagrelor	24	5	4.80 (1.83-12.58)	3	1	3.00 (0.31-28.84)
B01AC04	Clopidogrel	216	126	1.71 (1.38-2.14)	175	125	1.40 (1.11-1.76)
B01AB05	Enoxaparin	41	15	2.73 (1.51-4.94)	37	28	1.32 (0.81-2.16)
B01AC06	Acetylsalicylic acid	1448	1185	1.22 (1.13-1.32)	1693	1618	1.05 (0.98-1.12)
	<i>Antiadrenergic agents</i>						
R03AC03	Terbutaline	57	43	1.33 (0.89-1.97)	35	34	1.03 (0.64-1.65)
R03AC02	Salbutamol	343	281	1.22 (1.04-1.43)	310	251	1.24 (1.05-1.46)

Supplementary file

	<i>Proton pump inhibitors</i>						
A02BC05	Esomeprazol	305	307	0.99 (0.85-1.16)	420	281	1.49 (1.29-1.74)
A02BC01	Omeprazole	108	98	1.10 (0.84-1.45)	130	115	1.13 (0.88-1.45)
	<i>Vasodilator</i>						
C01DA02	Glyceral trinitrate	992	390	2.54 (2.26-2.86)	766	474	1.62 (1.44-1.81)
	<i>Prokinetic drug</i>						
A03FA01	Metoclopramide	132	98	1.35 (1.04-1.75)	203	122	1.66 (1.33-2.08)
	<i>Expectorants</i>						
R05CB01	Acetylcysteine	204	175	1.17 (0.95-1.43)	315	219	1.44 (1.21-1.71)
	<i>Anxiolytics</i>						
N05BA01	Diazepam	334	325	1.03 (0.88-1.20)	330	250	1.32 (1.12-1.56)
	<i>Angiotension II antagonists</i>						
C09CA01	Losartan	147	139	1.06 (0.84-1.33)	145	171	0.85 (0.68-1.06)
C09CA06	Candesartan	180	193	0.93 (0.76-1.14)	180	194	0.93 (0.76-1.14)
	<i>Antidepressants</i>						
N06AB04	Citalopram	63	56	1.13 (0.78-1.61)	107	126	0.85 (0.66-1.10)
N06AB06	Sertraline	30	34	0.68 (0.43-1.08)	60	54	1.11 (0.77-1.60)
	<i>ACE inhibitors</i>						
C09AA05	Ramipril	275	237	1.16 (0.98-1.38)	434	446	0.97 (0.85-1.11)
	<i>Antigout agent</i>						
M04AA01	Allopurinol	109	137	0.80 (0.62-1.02)	242	257	0.94 (0.79-1.12)
	<i>Antidiabetic agent</i>						
A10BA02	Metformin	361	367	0.98 (0.85-1.14)	332	328	1.01 (0.87-1.18)
	<i>Beta-blocking agents</i>						
C07AB02	Metoprolol	1101	925	1.19 (1.09-1.30)	1478	1364	1.09 (1.01-1.17)
C07AB03	Atenolol	96	111	0.86 (0.66-1.14)	156	174	0.90 (0.72-1.11)
	<i>Calcium-channel blockers</i>						
C08CA01	Amlodipine	329	331	0.99 (0.85-1.16)	377	387	0.97 (0.85-1.12)
C08CA02	Felodipine	58	38	1.53 (1.01-2.29)	54	55	0.98 (0.67-1.43)
	<i>Decongestants</i>						
R01AD09	Mometasone	62	72	0.86 (0.61-1.21)	21	28	0.75 (0.43-1.32)
	<i>Diuretics</i>						
C03CA01	Furosemide	317	301	1.05 (0.90-1.23)	1000	900	1.11 (1.02-1.22)
C03DA01	Spironolactone	72	66	1.09 (0.78-1.52)	186	153	1.22 (0.98-1.51)
	<i>Glucocorticoids</i>						
H02AB06	Prednisolone	438	362	1.21 (1.05-1.39)	525	461	1.14 (1.00-1.29)

Supplementary file

	<i>Hypnotics and sedatives</i>						
N05CF01	Zopiclone	608	568	1.07 (0.95-1.20)	1010	892	1.13 (1.03-1.24)
N05CF02	Zolpidem	76	77	0.99 (0.72-1.36)	608	568	1.07 (0.95-1.20)
	<i>Lipid modifying agent</i>						
C10AA01	Simvastatin	903	846	1.07 (0.97-1.17)	903	902	1.00 (0.91-1.10)
	<i>Antithyroid agent</i>						
H03AA01	Levothyroxine sodium	230	257	0.89 (0.75-1.07)	399	391	1.02 (0.89-1.17)
	<i>Antianemic agent</i>						
B03BA03	Hydroxocobalamin	20	18	1.11 (0.59-2.10)	29	45	0.64 (0.40-1.03)

NA= Not Available

* Case crossover analysis, case period (1 to 7 days) and control period (15 to 21 days) before the index-date for the diagnosis of first AMI.

† In BOLASSO, the effect of each selected drugs is controlled for the effect of other selected drugs.

‡ Data from the Norwegian Prescribed Database, 2004 to 2014

§ Classified according to Anatomical Therapeutic Chemical (ATC), 5th level

Table S6 Relative risks of acute myocardial infarction within 7 days after the drug was dispensed. Univariable results for drugs selected by BOLASSO approach in both the countries. Sub-group analyses according to age in Sweden

				Sweden [‡]			Sweden [‡]
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Supplementary file

				<80 years			≥80 years
ATC Code ^s	Drug Names	Case window (exposed); N	Control window (exposed); N	RR (95% CI)	Case window (exposed); N	Control window (exposed); N	RR (95% CI)
	<i>Narcotic analgesics</i>						
N02AG01	Morphine & antispasmodics	71	23	3.09 (1.93-4.94)	185	19	9.73 (6.07-15.61)
N02AA01	Morphine	665	537	1.23 (1.11-1.39)	1530	978	1.56 (1.44-1.70)
N02AA05	Oxycodone	1024	891	1.15 (1.05-1.26)	1635	1446	1.13 (1.05-1.23)
N02AA59	Codeine, combinations	929	873	1.06 (0.97-1.16)	597	518	1.16 (1.02-1.30)
R05FA02	Opium derivatives & expectorant	527	313	1.68 (1.46-1.94)	301	125	2.40 (1.95-2.97)
	<i>Non-narcotic analgesic</i>						
N02BE01	Paracetamol	4336	4304	1.01 (0.97-1.05)	10145	9732	1.04 (1.01-1.07)
	<i>Anti-inflammatory drugs</i>						
M01AB05	Diclofenac	838	968	1.20 (1.09-1.33)	342	303	1.12 (0.97-1.32)
	<i>Antibiotics</i>						
J01FA01	Erythromycin	66	24	2.75 (1.72-4.39)	24	12	2.00 (1.00-3.99)
J01AA02	Doxycycline	648	390	1.66 (1.47-1.88)	447	201	2.22 (1.88-2.63)
J01CA04	Amoxicillin	325	226	1.44 (1.21-1.70)	250	127	1.97 (1.59-2.44)
J01XE01	Nitrofurantoin	131	109	1.20 (0.93-1.55)	234	140	1.67 (1.36-2.06)
J01EA01	Trimethoprim	122	85	1.44 (1.09-1.89)	280	196	1.43 (1.19-1.71)
J01CE02	Phenoxymethylpenicillin	437	369	1.18 (1.03-1.36)	410	226	1.81 (1.54-2.13)
J01MA02	Ciprofloxacin	419	319	1.31 (1.14-1.52)	411	311	1.32 (1.14-1.53)
J01CA08	Pivmecillinam	159	137	1.16 (0.92-1.46)	376	285	1.31 (1.13-1.54)
	<i>Antiprotozoal drug</i>						
P01AB01	Metronidazole	75	93	0.81 (0.59-1.09)	94	92	1.02 (0.77-1.36)
	<i>Antithrombotic agents</i>						
B01AC24	Ticagrelor	81	11	7.36 (3.92-13.82)	15	3	5.00 (1.44-17.27)
B01AC04	Clopidogrel	704	391	1.80 (1.59-2.04)	586	461	1.27 (1.13-1.44)
B01AB05	Enoxaparin	58	53	1.09 (0.75-1.59)	68	40	1.70 (1.15-2.51)

Supplementary file

B01AC06	Acetylsalicylic acid	4956	4746	1.04 (1.00-1.09)	10,533	10,494	1.00 (0.98-1.03)
	<i>Antiadrenergic agents</i>						
R03AC03	Terbutaline	645	533	1.21 (1.08-1.36)	323	254	1.27 (1.08-1.50)
R03AC02	Salbutamol	418	346	1.21 (1.05-1.39)	200	180	1.11 (0.91-1.36)
	<i>Proton pump inhibitors</i>						
A02BC05	Esomeprazol	472	430	1.10 (0.96-1.25)	399	372	1.07 (0.93-1.24)
A02BC01	Omeprazole	3328	3012	1.10 (1.05-1.16)	5542	5249	1.06 (1.02-1.10)
	<i>Vasodilator</i>						
C01DA02	Glyceral trinitrate	2760	1456	1.90 (1.78-2.02)	2260	1493	1.51 (1.42-1.62)
	<i>Prokinetic drug</i>						
A03FA01	Metoclopramide	310	248	1.25 (1.06-1.48)	399	255	1.56 (1.34-1.83)
	<i>Expectorants</i>						
R05CB01	Acetylcysteine	828	649	1.28 (1.15-1.41)	849	726	1.17 (1.06-1.29)
	<i>Anxiolytics</i>						
N05BA01	Diazepam	669	596	1.12 (1.01-1.25)	496	361	1.37 (1.20-1.57)
	<i>Angiotension II antagonists</i>						
C09CA01	Losartan	772	767	1.01 (0.91-1.11)	956	971	0.98 (0.90-1.08)
C09CA06	Candesartan	648	684	0.95 (0.85-1.05)	715	764	0.94 (0.85-1.04)
	<i>Antidepressants</i>						
N06AB04	Citalopram	1439	1475	0.98 (0.91-1.05)	4109	4038	1.02 (0.97-1.05)
N06AB06	Sertraline	498	533	0.93 (0.83-1.06)	860	827	1.04 (0.95-1.14)
	<i>ACE inhibitors</i>						
C09AA05	Ramipril	738	726	1.01 (0.92-1.13)	1132	1129	1.00 (0.92-1.09)
	<i>Antigout agent</i>						
M04AA01	Allopurinol	597	651	0.92 (0.82-1.02)	1300	1301	0.99 (0.93-1.08)
	<i>Antidiabetic agent</i>						
A10BA02	Metformin	1501	1694	0.89 (0.83-1.04)	1158	1202	0.96 (0.89-1.04)
	<i>Beta-blocking agents</i>						

Supplementary file

C07AB02	Metoprolol	3324	3074	1.08 (1.03-1.14)	5537	5363	1.03 (0.99-1.07)
C07AB03	Atenolol	1092	1090	1.00 (0.92-1.09)	1744	1733	1.01 (0.94-1.08)
	Calcium-channel blockers						
C08CA01	Amlodipine	1163	1162	1.00 (0.92-1.09)	1349	1382	0.98 (0.91-1.05)
C08CA02	Felodipine	1382	1380	1.00 (0.93-1.08)	2147	2237	0.96 (0.90-1.02)
	Decongestants						
R01AD09	Mometasone	245	252	0.97 (0.82-1.16)	81	86	0.94 (0.70-1.28)
	Diuretics						
C03CA01	Furosemide	3329	3312	1.01 (0.96-1.05)	10978	10495	1.05 (1.02-1.07)
C03DA01	Spironolactone	743	761	0.98 (0.88-1.08)	1973	1913	1.03 (0.97-1.10)
	Glucocorticoids						
H02AB06	Prednisolone	1330	1184	1.12 (1.04-1.21)	2362	2302	1.03 (0.97-1.09)
	Hypnotics and sedatives						
N05CF01	Zopiclone	1898	1938	0.98 (0.92-1.04)	4101	4086	1.00 (0.96-1.05)
N05CF02	Zolpidem	932	980	0.95 (0.87-1.04)	1623	1584	1.02 (0.96-1.10)
	Lipid modifying agent						
C10AA01	Simvastatin	3239	3233	1.00 (0.95-1.05)	2372	2439	0.97 (0.92-1.03)
	Antithyroid agent						
H03AA01	Levothyroxine sodium	1326	1351	0.98 (0.91-1.06)	3517	3512	1.00 (0.96-1.05)
	Antianemic agent						
B03BA03	Hydroxocobalamin	34	66	0.52 (0.34-0.78)	91	89	1.02 (0.76-1.37)

* Case crossover analysis, case period (1 to 7 days) and control period (15 to 21 days) before the index-date for the diagnosis of first AMI.

† In BOLASSO, the effect of each selected drugs is controlled for the effect of other selected drugs.

‡ Data from the Swedish Prescribed Drug Register, 2005 to 2014

§ Classified according to Anatomical Therapeutic Chemical (ATC), 5th level

Appendix A

The case-crossover design

A.1 The likelihood function under the case-crossover design

In our analysis, the subjects are the patients who experienced the event (case), and each patient is both the case and the control of itself, in different time periods. For the whole analysis, we used one case and one control window for each patient. According to [6], our design is called a non-localizable design and, more specifically, an unidirectional design, because the windows are placed after observing the event for each patient and not a priori.

Assume that we have a total of N individuals who experienced the event at some point in the time set $\{1, \dots, T\}$. Here, T is the length of the observation period, and the $t \in \{1, \dots, T\}$ are the discrete time points where each case was checked (followed up). Let Y_{it} be the risk occurrence indicator for subject i at time t , that is $Y_{it} = 1$ if the event took place at time t and $Y_{it} = 0$ otherwise. For $i = 1, \dots, N$ and $t = 1, \dots, T$, let $X_{it} = (X_{it1}, \dots, X_{itp})$ be the p -dimensional vector of exposures at time t for the i th subject. Let further $X_i = (X_{it}; t = 1, \dots, T)$ be the corresponding p -dimensional exposure time series vector.

Then, if it is assumed that events follow a proportional hazards model, and if it is assumed that events are rare, we will assume that

$$P(Y_{it} = 1 | X_i) = \lambda_{0it} e^{X_{it}\beta}, \quad (1)$$

where $\beta = (\beta_1, \dots, \beta_p)'$ is a vector of coefficients. The baseline function λ_{0it} is assumed to vary among subjects, carrying characteristics of the i th subject like, for example, age, or other characteristics which may change with time t . In other words, Eq. (1) is the probability that the i th subject will experience the event exactly at time t , given its exposure vector and characteristics.

Assume first that the exposure of each subject is observed throughout the time set $\{1, 2, \dots, T\}$. Then by conditioning on the occurrence of exactly one event in $\{1, 2, \dots, T\}$, and as above assuming that events are rare, the contribution to the likelihood from the i th subject would be ([8, 6]):

$$\begin{aligned} & P\left(Y_{i,t_i} = 1 \mid \sum_{s=1}^T Y_{is} = 1, X_i\right) \\ &= \frac{P(Y_{i,t_i} = 1 | X_i)}{P\left(\sum_{s=1}^T Y_{is} = 1 | X_i\right)} \\ &= \frac{P(Y_{i,t_i} = 1 | X_i)}{\sum_{s=1}^T P(Y_{is} = 1 | X_i)} \end{aligned}$$

$$= \frac{\lambda_{0it_i} e^{X_{it_i}\beta}}{\sum_{s=1}^T \lambda_{0is} e^{X_{is}\beta}} \quad (2)$$

The complete likelihood is then the product of these contributions, namely

$$L(\beta) = \prod_{i=1}^N \frac{\lambda_{0it_i} e^{X_{it_i}\beta}}{\sum_{s=1}^T \lambda_{0is} e^{X_{is}\beta}}. \quad (3)$$

Since we do not know the exposure X_{it} for all $t \in 1, 2, \dots, T$, but only in a referent window W_i , following Lumley and Levy [8], we replace the denominators in Eq. (3) by the simplification where s runs only in the referent window. Thus, we replace Eq. (3) by

$$L(\beta) = \prod_{i=1}^N \frac{\lambda_{0it_i} e^{X_{it_i}\beta}}{\sum_{t \in W_i} \lambda_{0it} e^{X_{it}\beta}} = \prod_{i=1}^N \frac{e^{X_{it_i}\beta}}{\sum_{t \in W_i} e^{X_{it}\beta}} = \prod_{i=1}^N \frac{e^{X_{it_i}\beta}}{e^{X_{it_i}\beta} + e^{X_{is_i}\beta}}. \quad (4)$$

In our application, $W_i = \{t_i, s_i\}$, where t_i and s_i are the case and the control windows of the i th subject, respectively. Furthermore, the λ_{0it_i} and λ_{0it} are cancelled because they are assumed to be (approximately) constant in the referent windows. Now, X_{it_i} is a vector of length p corresponding to the exposure of each drug in the case window, while X_{is_i} is a vector of the same length corresponding to the exposures in the control window. Both vectors contain the values 0 and 1 for non-exposure and exposure, respectively.

It should be noted that Eq. (4) is not an actual likelihood because of the reduction of the sum in the denominator of (3). Thus, as noted by Lumley and Levy [8], the resulting estimates may be biased. This bias, called overlap bias, will however usually be small (see [8]).

On the other hand, Eq. (4) has the form of the likelihood of a conditional logistic regression (CLR) and can hence be analyzed using standard statistical packages allowing CLR. Note that the window W_i in Eq. (4) consists of two time points, t_i (case) and s_i (control), while more controls can be included by adding points in the window.

A.2 Generalized linear model

Our model can be represented differently in order to show that it is a generalized linear model of logistic type. Consider the matrices $X_t = (X_{1t_1}, \dots, X_{Nt_N})^T$, corresponding to the case windows, and $X_s = (X_{1s_1}, \dots, X_{Ns_N})^T$, corresponding to the control windows, both of dimension $N \times p$, where X_{it_i} and X_{is_i} are defined above. Consider also the corresponding response vectors $Y_t = (Y_{1t_1}, \dots, Y_{Nt_N})^T$ and $Y_s = (Y_{1s_1}, \dots, Y_{Ns_N})^T$, for the cases and controls, respectively. These are both N -dimensional, where the response vector for the cases contains only the element 1 and the response vector for the controls contains only the element 0. This is because we restrict attention to patients with exactly one event in the

given time set. The likelihood $L(\beta)$ can hence be written in the form

$$L(\beta) = \prod_{i=1}^N \frac{e^{X_{it_i}\beta}}{e^{X_{it_i}\beta} + e^{X_{is_i}\beta}} = \prod_{i=1}^N \frac{1}{1 + e^{-X_i\beta}}, \quad (5)$$

where $X_i = X_{it_i} - X_{is_i}$, that is, we subtract the control vector from the case vector for each patient. As will be seen below, for a case-crossover design with one case and one control window, the likelihood can be written in the form of the unconditional likelihood for a binary logistic regression with no intercept and constant response equal to one (see Avalos et al.[3]). The fact that the response is constant and equal to one, becomes more clear when we subtract the response vector Y_s from Y_t . Note that now the data matrix X consists of values $-1, 0, 1$. Furthermore, for a specific component β_j of the vector β , e^{β_j} is the relative risk for the event, if the j th component of X_i is increased by 1, which means that the corresponding medicine is taken in the case window and not in the control window.

By letting p_i be the contribution of the i th individual to the likelihood in Eq. (5), that is $p_i = \frac{1}{1+e^{-X_i\beta}} = \frac{e^{X_i\beta}}{1+e^{X_i\beta}}$, then the likelihood can be written in the following form:

$$L(\beta) = \prod_{i=1}^N \frac{1}{1 + e^{-X_i\beta}} = \prod_{i=1}^N p_i = \prod_{i=1}^N p_i^{y_i} (1 - p_i)^{1-y_i}, \quad (6)$$

since $y_i = 1$ for all i . The log-likelihood is of the form

$$\begin{aligned} \ell(\beta) &= \log(L(\beta)) = \sum_{i=1}^N \log [p_i^{y_i} (1 - p_i)^{1-y_i}] \\ &= \sum_{i=1}^N [y_i \log(p_i) + (1 - y_i) \log(1 - p_i)] \\ &= \sum_{i=1}^N [y_i \text{logit}(p_i) + \log(1 - p_i)], \end{aligned} \quad (7)$$

which corresponds to the likelihood of logistic regression ([9, 10])

Finally, the log-likelihood function given in Eq. (7) is a concave function with respect to the β coefficients. This can easily be seen by rewriting the function in the following form,

$$\begin{aligned} \ell(\beta) &= \sum_{i=1}^N [y_i \text{logit}(p_i) + \log(1 - p_i)] \\ &= \sum_{i=1}^N \left(y_i X_i \beta + \log \left(\frac{1}{1 + e^{X_i \beta}} \right) \right) \\ &= \sum_{i=1}^N \left(y_i X_i \beta - \log \left(1 + e^{X_i \beta} \right) \right) \end{aligned}$$

and noting that $-\log(1 + e^x)$ is a concave function.

A.3 The lasso method and glmnet

In this section we describe how we estimated the coefficients in β using the lasso (the least absolute shrinkage and selection operator) method ([11]). More specifically, we estimated the coefficients under the lasso penalty by minimizing the negative penalized log-likelihood in Eq. (7), that is,

$$\hat{\beta}(\lambda) = \operatorname{argmin}_{\beta} \left(-\ell(\beta) + \lambda \sum_j |\beta_j| \right).$$

The estimation was done via a coordinate descent algorithm using the glmnet package ([5]) in the statistical package R. We chose the binomial family with logit link function in the settings of the glmnet function. Furthermore, the choice of λ was done by generating a sequence of 100 λ values and then choosing the best, using 10-fold cross-validation. All of those functions are provided by the package.

The glmnet function for the binomial model requires a two-level response. In our case we have, however, a constant response equal to one. To overcome this problem and allow the use the glmnet function, we added N rows of zeros to the data matrix X , and N new observations to the response vector Y , all with the value zero. We demonstrate below that this does not change the likelihood function, and since the response vector now contains both zeros and ones, the estimation of β can be done using the glmnet function,

To see why the above claim is true, let j correspond to lines of the extended data matrix X which were added, while i corresponds to lines of the original data matrix. Then $p_j = 1/(1 + e^0) = 1/2$, while $p_i = \frac{1}{1 + e^{-X_i\beta}}$, as before. Hence the likelihood in Eq. (6), using the extended data matrix, becomes

$$L(\beta) = \prod_{j=1}^N p_j^{y_j} (1-p_j)^{1-y_j} \prod_{i=1}^N p_i^{y_i} (1-p_i)^{1-y_i} = \prod_{j=1}^N (1-p_j) \prod_{i=1}^N p_i = (1/2)^N \prod_{i=1}^N p_i, \quad (8)$$

which equals the original likelihood in Eq. (6) multiplied by a constant independent of the parameters. Hence, the estimated coefficients are not affected by the modification. We chose N additional observations with zero response because, as we will discuss in Appendix A.4, we use bootstrapping to sample from the data matrix X . We found that N extra observations are enough to ensure both 0 and 1 responses in each bootstrap sample. If we alternatively added, say, only one extra observation, we would most probably get some bootstrap samples with only 1 as a response, and thus the glmnet function would not work. However, as already noted, the actual number of extra observations with zero response does generally not affect the estimated coefficients.

A.4 Bolasso

Lasso sometimes allows a few irrelevant variables to enter the model ([3]). Further, according to Tibshirani [11], the standard errors for the lasso estimates

are difficult to acquire. Those problems can be reduced by bootstrapping. Tibshirani [11], Avalos et al. [3] and Avalos et al. [2] suggested a bootstrap version of lasso which is called bolasso, which reduces the uncertainties of the lasso estimates. Bolasso runs a bootstrap on many samples, and estimates the parameters for each sample, using the lasso approach.

In our analysis we ran a bootstrap on the lasso model described in Section A.3, using 1000 bootstrap samples. For each bootstrap sample, a new λ sequence was generated by the glmnet package and the optimal λ was chosen using 10-fold cross validation. Then the model was fitted by glmnet using the current bootstrap sample.

The β -coefficients frequently selected by the lasso from the bootstrap samples are taken into account, while the others are set to zero [3]. Avalos et al. [3] suggested using Akaike's information criterion ([1]), $AIC = -2\ell(\hat{\beta}) + 2k$, for estimating the frequency threshold of bolasso. Here $\ell(\hat{\beta})$ is the log-likelihood function applied on the estimated coefficients from each model under selection, and k is the total number of non-zero elements in the β vector. AIC corresponds to an estimation of the allowed number of times that a coefficient could have been set to zero among the bootstraps. We can compute the AIC for different models and then choose the model which gives the lowest AIC -value.

The output from the bolasso in our analysis is a matrix of dimension $p \times B$. Each column of the matrix corresponds to one bootstrap replicate, that is, the estimated vector of coefficients from that bootstrap sample. Each row of the matrix corresponds to the values that the specific coefficient took among the bootstrap samples. For each row in the matrix, we computed the total number of zeros and we created a frequency vector of length p . For each value in the frequency vector we created a model by checking which of the coefficients had been set to zero less times than the chosen threshold. For those, their mean among the bootstraps was taken as an estimate, that is

$$\hat{\beta}_j = \sum_{b=1}^B \beta_j^{*b} / B,$$

where β_j^{*b} is the b -th bootstrap estimate of coefficient β_j and B is the total number of bootstrap replicates ([4]). The other coefficients are simply set to zero. Next, the AIC was computed for the corresponding model, where k is the number of non-zero estimates in the newly computed β vector. Finally, this is done for all thresholds in the sequence and the one which gives the lowest AIC is chosen as optimal. For that optimal threshold we again check which of the coefficients have been set to zero less times than the optimal threshold and we compute $\hat{\beta}_j$ as before, while the others are set to zero. This vector of coefficients is the bolasso estimate of the coefficients for the objective function ([3]).

Finally, we can compute the standard error of each coefficient as

$$S\hat{D}_j = \left(\sum_{b=1}^B (\beta_j^{*b} - \hat{\beta}_j)^2 / (B - 1) \right)^{1/2},$$

as well as 95% confidence intervals based on the central limit theorem ($\hat{\beta}_j - 1.96S\hat{D}_j, \hat{\beta}_j + 1.96S\hat{D}_j$) ([4]). However, according to Lockhart et al. [7], con-

fidence intervals obtained by the bootstrap estimates are not optimal for the lasso.

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