

Supplemental Table 1 (online only). Codes for outcome definitions

Outcome	Code Type	Code	Description
Myocardial infarction	ICD-9 diagnosis	410.xx	Acute myocardial infarction
Myocardial ischemia	ICD-9 diagnosis	414.xx (excluding 414.1x)	Other forms of chronic ischemic heart disease (excluding aneurysm and dissection of heart)
Unstable angina	ICD-9 diagnosis	411.1	Intermediate coronary syndrome
	ICD-9 diagnosis	411.8, 411.81, 411.89	Other acute coronary occlusion
	ICD-9 proc	36.33	Endoscopic transmyocardial revascularization
	ICD-9 proc	36.03	Open chest coronary artery angioplasty
	ICD-9 proc	36.09	Other removal of coronary artery obstruction
	ICD-9 proc	36.1x	Aortocoronary bypass for heart revascularization
	ICD-9 proc	36.2	Heart revascularization by arterial implant
	ICD-9 proc	36.31	Open chest transmyocardial revascularization
	ICD-9 proc	36.07	Insertion of drug-eluting coronary artery stent(s)
	ICD-9 proc	36.34	Percutaneous transmyocardial revascularization
	ICD-9 proc	36.32	Other transmyocardial revascularization
	ICD-9 proc	36.39	Other heart revascularization
	CPT	33141	Transmyocardial laser revascularization, by thoracotomy; performed at the time of other open cardiac procedure(s)
	CPT	33508	Endoscopy, surgical, including video-assisted harvest of vein(s) for coronary artery bypass procedure
	CPT	33517 – 33519, 33521 – 33523	Coronary artery bypass, using venous graft(s) and arterial graft(s)
	CPT	33530	Reoperation, coronary artery bypass procedure or valve procedure, more than 1 month after original operation
	CPT	33572	Coronary endarterectomy, open, any method, of left anterior descending, circumflex, or right coronary artery performed in conjunction with coronary artery bypass graft procedure, each vessel
	CPT	35500	Harvest of upper extremity vein, 1 segment, for lower extremity or coronary artery bypass procedure
	CPT	35572	Harvest of femoropopliteal vein, 1 segment, for vascular reconstruction procedure (e.g., aortic, vena caval, coronary, peripheral artery)
	CPT	35600	Harvest of upper extremity artery, 1 segment, for coronary artery bypass procedure
	CPT	00566	Anesthesia for direct coronary artery bypass grafting; without pump oxygenator
	CPT	00567	Anesthesia for direct coronary artery bypass grafting; with pump oxygenator
	CPT	33140	Transmyocardial laser revascularization, by thoracotomy; (separate procedure)
	CPT	33510 – 33516	Coronary artery bypass, vein only
	CPT	33533 – 33536	Coronary artery bypass, using arterial graft(s)

	CPT	92973	Percutaneous transluminal coronary thrombectomy
	CPT	92980	Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel
	CPT	92981	Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel
	CPT	92982	Percutaneous transluminal coronary balloon angioplasty; single vessel
	CPT	92984	Percutaneous transluminal coronary balloon angioplasty; each additional vessel
	CPT	92996	Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty; each additional vessel
	CPT	92975	Thrombolysis, coronary; by intracoronary infusion, including selective coronary angiography
	CPT	92977	Thrombolysis, coronary; by intravenous infusion
	CPT	92995	Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty; single vessel
	HCPCS	S2205 – S2209	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision
	HCPCS	C9600 – C9606	Percutaneous transcatheter placement of drug-eluting intracoronary stent(s), with coronary angioplasty when performed
	HCPCS	G0290	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel
	HCPCS	G0291	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel
Ischemic stroke	ICD-9 diagnosis	433.x1	Occlusion and stenosis of precerebral arteries, with cerebral infarction
	ICD-9 diagnosis	434.x1	Occlusion of cerebral arteries, with cerebral infarction
Hemorrhagic stroke	ICD-9 diagnosis	430	Subarachnoid hemorrhage
	ICD-9 diagnosis	431	Intracerebral hemorrhage
	ICD-9 diagnosis	432.0	Nontraumatic extradural hemorrhage
	ICD-9 diagnosis	432.1	Subdural hemorrhage
	ICD-9 diagnosis	432.9	Unspecified intracranial hemorrhage
Transient ischemic attack	ICD-9 diagnosis	435.x	Transient cerebral ischemia
Mortality from cardiovascular/cerebrovascular causes	ICD-10 diagnosis	I21.x	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
	ICD-10 diagnosis	I22.x	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
	ICD-10 diagnosis	I25.x (excluding	Chronic ischemic heart disease (excluding

		I25.3 and I25.4)	aneurysm and dissection of heart)
	ICD-10 diagnosis	I20.0	Unstable angina
	ICD-10 diagnosis	I24.0	Acute coronary thrombosis not resulting in myocardial infarction
	ICD-10 diagnosis	I24.9	Acute ischemic heart disease, unspecified
	ICD-10 diagnosis	I24.8	Other forms of acute ischemic heart disease
	ICD-10 diagnosis	I63.x	Cerebral infarction, due to occlusion and stenosis of cerebral and precerebral arteries
	ICD-10 diagnosis	I60.x	Nontraumatic subarachnoid hemorrhage
	ICD-10 diagnosis	I62.x	Other and unspecified nontraumatic intracranial hemorrhage
	ICD-10 diagnosis	G45.x	Transient cerebral ischemic attacks and related syndromes
Mortality from trauma	ICD-10 diagnosis	S00.x-S09.x	Injuries to the head
	ICD-10 diagnosis	S10.x-S19.x	Injuries to the neck
	ICD-10 diagnosis	S20.x-S29.x	Injuries to the thorax
	ICD-10 diagnosis	S30.x-S39.x	Injuries to the abdomen, lower back, lumbar spine, pelvis and external genitals
	ICD-10 diagnosis	S40.x-S49.x	Injuries to the shoulder and upper arm
	ICD-10 diagnosis	S50.x-S59.x	Injuries to the elbow and forearm
	ICD-10 diagnosis	S60.x-S69.x	Injuries to the wrist, hand and fingers
	ICD-10 diagnosis	S70.x-S79.x	Injuries to the hip and thigh
	ICD-10 diagnosis	S80.x-S89.x	Injuries to the knee and lower leg
	ICD-10 diagnosis	S90.x-S99.x	Injuries to the ankle and foot
	ICD-10 diagnosis	T07.x	Injuries involving multiple body regions
	ICD-10 diagnosis	T14.x	Injury of unspecified body region
	ICD-10 diagnosis	T15.x-T19.x	Effects of foreign body entering through natural orifice
	ICD-10 diagnosis	T20.x-T25.x	Burns and corrosions of external body surface, specified by site
	ICD-10 diagnosis	T26.x-T28.x	Burns and corrosions confined to eye and internal organs
	ICD-10 diagnosis	T30.x-T32.x	Burns and corrosions of multiple and unspecified body regions
	ICD-10 diagnosis	T33.x-T34.x	Frostbite
	ICD-10 diagnosis	T51.x - T65.x	Toxic effects of substances chiefly nonmedicinal as to source
	ICD-10 diagnosis	T66.x - T78.x	Other and unspecified effects of external causes
	ICD-10 diagnosis	T79.x	Certain early complications of trauma
	ICD-10 diagnosis	V01.x - V99.x	Transport accidents
	ICD-10 diagnosis	W00.x - X59.x	Other external causes of accidental injury
	ICD-10 diagnosis	X65.x - X69.x	Intentional self-poisoning from nonmedicinal substances
	ICD-10 diagnosis	X70.x - X84.x	Intentional self-harm
	ICD-10 diagnosis	X86.x - Y09.x	Assault
	ICD-10 diagnosis	Y20.x - Y34.x	Harm - undetermined intent
		Y35.x - Y36.x	Injury due to legal intervention or war operations
Mortality ascribed to drug	ICD-10 diagnosis	T36.x - T50.x	Poisoning by, adverse effect of and underdosing

overdose			of drugs, medicaments and biological substances
	ICD-10 diagnosis	X60.x - X64.x	Intentional self-poisoning from medicinal substances
	ICD-10 diagnosis	X85.x	Assault by drugs, medicaments, and biological substances
	ICD-10 diagnosis	Y10.x - Y19.x	Poisoning, undetermined intent

Supplemental Table 2. Variables included in the propensity score models for the migraine study population initiating prophylactic treatments

	Topiramate vs. Cardiovascular Treatments	Topiramate vs. Anti-depressants	Topiramate vs. Other Anti-convulsants	Topiramate vs. Other Prophylactic Treatments
Pre-defined covariates				
Age groups (18-24, 25-44, 35-44, 45-54, 55-64, 65+)	x	x	x	x
Age (continuous)	x	x	x	x
Sex	x	x	x	x
Geographic region	x	x	x	x
Calendar year	x	x	x	x
Calendar month (January-March, April-June, July-September, October-December)	x	x	x	x
Hypertension	x	x	x	x
Hypercholesterolemia	x	x	x	x
Hypertension by calendar year	x	x	x	x
Hypercholesterolemia by calendar year	x	x	x	x
Age (continuous) by calendar year	x	x	x	x
ACE inhibitors (excluding drug initiation date)	x	x	x	x
ARBs (excluding drug initiation date)	x	x	x	x
Beta-blockers (excluding drug initiation date)		x	x	x
Anti-depressants (excluding drug initiation date)			x	x
Anti-arrhythmics	x			
Aspirin/dipyridamole	x			
Dalteparin		x	x	x
Fondaparinux		x	x	x
Thiazide		x	x	x
SNRIs (excluding drug initiation date)	x		x	x
Sympatholytic hypotensives (excluding drug initiation date)		x	x	x
Alpha blockers	x	x	x	x
Loop diuretics	x			
Nitroglycerin	x	x	x	x
Other anticonvulsant use (excluding drug initiation date)	x	x		x
Other prophylactic treatments (excluding drug initiation date)	x	x	x	
Potassium sparing diuretics	x			
Migraine aura	x	x	x	x

Cardiac arrhythmia	x	x	x	x
Congestive heart failure	x	x	x	x
Depression	x			
Obesity	x	x	x	x
Pregnancy, non-delivery indicators, within 30 days prior	x	x	x	x
Renal disease	x			
Unstable angina/coronary revascularization	x	x	x	x
Number of physician visits (continuous)	x			
Number of unique medications dispensed (continuous)	x	x	x	x
Number of procedures (continuous)	x			
Switch new user of prophylactic treatment	x	x	x	x
Emergency room visit within 30 days of prophylactic treatment		x	x	x
Hospitalization within 30 days of prophylactic treatment initiation	x	x	x	x
Total costs (\$) (continuous)		x	x	x
Empirically identified covariates				
<i>Diagnoses</i>	x			
Viral and chlamydial infection in conditions classified elsewhere and of specific site (ICD-9 079)		x	x	x
Benign neoplasm of skin (ICD-9 216)	x	x	x	x
Episodic mood disorders (ICD-9 296)		x	x	x
Anxiety, dissociative and somatoform disorders (ICD-9 300)	x	x	x	x
Special symptoms or syndromes, not elsewhere classified (ICD-9 307)		x	x	x
Depressive disorder, not elsewhere classified (ICD-9 311)		x	x	x
Organic sleep disorders (ICD-9 327)	x	x	x	x
Migraine (ICD-9 346)	x	x	x	x
Other disorders of brain (ICD-9 348)		x	x	x
Mononeuritis of upper limb and mononeuritis multiplex (ICD-9 354)	x			
Other disorders of eye (ICD-9 379)	x	x	x	x
Cardiac dysrhythmias (ICD-9 427)	x			
Acute sinusitis (ICD-9 461)		x	x	x
Chronic sinusitis (ICD-9 473)	x			
Other diseases of upper respiratory tract (ICD-9 478)		x	x	x
Functional digestive disorders, not elsewhere classified (ICD-9 564)		x	x	x

Menopausal and postmenopausal disorders (ICD-9 627)	x	x	x	x
Diseases of sebaceous glands (ICD-9 706)	x			
Osteoarthritis and allied disorders (ICD-9 715)	x	x	x	x
Other and unspecified disorders of joint (ICD-9 719)	x	x	x	x
Spondylosis and allied disorders (ICD-9 721)	x			
Other disorders of bone and cartilage (ICD-9 733)		x	x	x
General symptoms (ICD-9 780)	x			
Symptoms involving nervous and musculoskeletal systems (ICD-9 781)	x			
Symptoms involving skin and other integumentary tissue (ICD-9 782)		x	x	x
Symptoms concerning nutrition, metabolism, and development (ICD-9 783)	x	x	x	x
Symptoms involving head and neck (ICD-9 784)	x	x	x	x
Symptoms involving cardiovascular system (ICD-9 785)	x	x	x	x
Nonspecific abnormal results of function studies (ICD-9 794)	x			
Other nonspecific abnormal findings (ICD-9 796)	x	x	x	x
Sprains and strains of other and unspecified parts of back (ICD-9 847)	x			
Contraceptive management (ICD-9 V25)	x	x	x	x
Other postprocedural status (ICD-9 V45)	x			x
General medical examination (ICD-9 V70)		x	x	x
Special screening for malignant neoplasms (ICD-9 V76)	x	x	x	x
<i>Medications</i>	x			
Estradiol	x			
Levonorgestrel-ethinyl estradiol	x	x	x	x
Alprazolam		x	x	x
Amitriptyline HCl			x	x
Nortriptyline HCl	x		x	x
Acetaminophen/caffeine/butalbital	x	x	x	x
Divalproex sodium	x	x		x
Clonazepam	x			
Benzonatate	x			

Carisoprodol	x			
Metformin HCl		x	x	x
Lorazepam		x	x	x
Ketorolac tromethamine		x	x	x
Baclofen	x			
Albuterol sulfate	x			
Prednisone	x			
Ibuprofen	x			
Propranolol HCl		x	x	x
Prednisone		x	x	x
Penicillin V potassium	x			
Mometasone furoate		x	x	x
Amoxicillin trihydrate	x			
Clindamycin HCl	x			
Amphetamine/dextroamphetamine		x	x	x
Metoprolol succinate		x	x	x
Phenazopyridine HCl	x			
Ciprofloxacin HCl	x	x	x	x
Seraltine HCl	x			
Fluticasone propionate	x			
Tramadol HCl	x	x	x	x
Promethazine HCl	x			
Zolmitriptan	x			
Cephalexin monohydrate	x			
Ondansetron	x			
Fluticasone/salmeterol	x	x	x	x
Oseltamivir phosphate	x			
Ethinyl estradiol/Drospirenone		x	x	x
Pantoprazole sodium	x			
Sumatriptan succinate		x	x	x
Rizatriptan benzoate		x	x	x
Eletriptan HBR	x			
<i>Procedures</i>	x			
Computed tomography, head or brain; without contrast material (CPT 70450)	x	x	x	x
Magnetic resonance imaging, brain; without contrast material (CPT 70551)	x	x	x	x
Magnetic resonance imaging, brain; without contrast material, followed by contrast material(s) and further sequences (CPT 70553)	x	x	x	x
Vitamin D; 25 hydroxy (CPT 82306)		x	x	x
Cyanocobalamin (Vitamin B-12) (CPT 82607)	x	x	x	x
Troponin, quantitative (CPT 84484)		x	x	x

Sedimentation rate, erythrocyte; automated (CPT 85652)		X	X	X
Culture, bacterial; quantitative colony count, urine (CPT 87086)		X	X	X
Routine electrocardiogram with at least 12 leads; with interpretation and report (CPT 93000)	X	X	X	X
Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular (CPT 96372)		X	X	X
Office or other outpatient visit for the evaluation and management of a new patient. Typically, 45 minutes are spent face-to-face with the patient and/or family (CPT 99204)	X	X	X	X
Office or other outpatient visit for the evaluation and management of an established patient. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services (CPT 99211)	X	X	X	X
Office or other outpatient visit for the evaluation and management of an established patient. Usually, the presenting problem(s) are self-limited or minor. Typically, 10 minutes are spent face-to-face with the patient and/or family (CPT 99212)	X	X	X	X
Office or other outpatient visit for the evaluation and management of an established patient. Usually, the presenting problem(s) are of low to moderate severity. Typically, 15 minutes are spent face-to-face with the patient and/or family (CPT 99213)	X			
Office or other outpatient visit for the evaluation and management of an established patient. Usually, the presenting problem(s) are of moderate to high severity. Typically, 25 minutes are spent face-to-face with the patient and/or family (CPT 99214)	X			
Office consultation for a new or established patient. Usually, the presenting problem(s) are of moderate to high severity. Typically, 60 minutes are spent face-to-face with the patient and/or family (CPT 99244)	X	X	X	X

Office consultation for a new or established patient. Usually, the presenting problem(s) are of moderate to high severity. Typically, 80 minutes are spent face-to-face with the patient and/or family (CPT 99245)	x	x	x	x
Injection, ketorolac tromethamine, per 15 mg (HCPCS J1885)		x	x	x
Injection, ondansetron HCl, per 1 mg (HCPCS J2405)	x	x	x	x

Supplemental Table 3 (online only). Retrospective cohort analysis: select characteristics of the subset of the migraine study population initiating prophylactic treatment occurring in the 12 months prior to treatment initiation who were unable to be matched on propensity score

	Comparison 1		Comparison 2		Comparison 3		Comparison 4	
	Topiramate (N =3,191)	Cardiovascular (N =4,152)	Topiramate (N =1,701)	Antidepressants (N =3,747)	Topiramate (N =4,657)	Anticonvulsants (N =2,230)	Topiramate (N =7,589)	Other (N =373)
Age in years* (mean, standard deviation)	36.7 (10.5)	49.4 (10.1)	35.6 (10.0)	47.3 (11.0)	35.6 (10.4)	50.2 (10.0)	38.0 (11.2)	50.4 (9.9)
Female* (n, %)	2,944 (92.3)	2,936 (70.7)	1,505 (88.5)	3,124 (83.4)	4,219 (90.6)	1,718 (77.0)	6,572 (86.6)	302 (81.0)
Prophylactic treatment history (n, %)								
Naïve new user	1,969 (61.7)	2,275 (54.8)	1,220 (71.7)	1,276 (34.1)	3,337 (71.7)	535 (24.0)	4,728 (62.3)	30 (8.0)
Switch new user	1,222 (38.3)	1,877 (45.2)	481 (28.3)	2,471 (65.9)	1,320 (28.3)	1,695 (76.0)	2,861 (37.7)	343 (92.0)
Healthcare utilization (mean, standard deviation)								
Number of physician visits	10.8 (8.5)	12.9 (14.2)	9.3 (6.8)	16.0 (15.9)	8.8 (5.9)	19.2 (15.8)	10.1 (8.0)	24.1 (27.8)
Number of emergency department visits	2.0 (4.8)	2.2 (5.6)	1.6 (4.0)	2.8 (6.7)	1.6 (4.0)	3.1 (7.1)	1.9 (4.7)	4.0 (8.7)
Number of hospitalizations	0.1 (0.4)	0.3 (0.8)	0.1 (0.4)	0.3 (0.8)	0.1 (0.3)	0.5 (1.1)	0.1 (0.4)	0.7 (1.7)
Other medications (n, %)								
Opioids	1,699 (53.2)	2,280 (54.9)	762 (44.8)	2,654 (70.8)	1,993 (42.8)	1,812 (81.3)	3,634 (47.9)	317 (85.0)
Prescription NSAIDs	1,228 (38.5)	1,403 (33.8)	569 (33.5)	1,709 (45.6)	1,432 (30.7)	1,169 (52.4)	2,583 (34.0)	201 (53.9)
Antihyperlipidemics	178 (5.6)	1,068 (25.7)	125 (7.3)	700 (18.7)	244 (5.2)	528 (23.7)	618 (8.1)	98 (26.3)
Hormone replacement therapy	227 (7.1)	455 (11.0)	58 (3.4)	636 (17.0)	207 (4.4)	395 (17.7)	453 (6.0)	98 (26.3)
Triptan use†								
Eletriptan	330 (10.3)	492 (11.8)	NR	NR	NR	NR	NR	NR
Zolmitriptan	64 (2.0)	180 (4.3)	NR	NR	NR	NR	NR	NR
Sumatriptan	NR	NR	694 (40.8)	1,309 (34.9)	2,088 (44.8)	611 (27.4)	3,074 (40.5)	97 (26.0)
Rizatriptan	NR	NR	206 (12.1)	431 (11.5)	649 (13.9)	195 (8.7)	956 (12.6)	52 (13.9)
Co-morbidities (n, %)								
Depression	724 (22.7)	988 (23.8)	186 (10.9)	1,738 (46.4)	807 (17.3)	902 (40.4)	1,575 (20.8)	159 (42.6)
Hypertension	174 (5.5)	3,258 (78.5)	431 (25.3)	1,059 (28.3)	690 (14.8)	915 (41.0)	1,479 (19.5)	158 (42.4)
Hypercholesterolemia	557 (17.5)	1,866 (44.9)	397 (23.3)	1,257 (33.5)	832 (17.9)	872 (39.1)	1,615 (21.3)	142 (38.1)
Cardiac arrhythmia	90 (2.8)	723 (17.4)	78 (4.6)	267 (7.1)	139 (3.0)	269 (12.1)	342 (4.5)	38 (10.2)
Obesity	422 (13.2)	523 (12.6)	390 (22.9)	292 (7.8)	621 (13.3)	264 (11.8)	1,056 (13.9)	37 (9.9)
Asthma	356 (11.2)	431 (10.4)	162 (9.5)	489 (13.1)	372 (8.0)	376 (16.9)	734 (9.7)	55 (14.7)
Pregnancy								
Delivery indicators	97 (3.0)	52 (1.3)	57 (3.4)	53 (1.4)	139 (3.0)	27 (1.2)	205 (2.7)	4 (1.1)
Non-delivery indicators‡	148 (4.6)	86 (2.1)	76 (4.5)	106 (2.8)	207 (4.4)	53 (2.4)	289 (3.8)	8 (2.1)

Abbreviations: NSAIDs, nonsteroidal antiinflammatory drugs; NR, not reported

*Age and sex were assessed on the day of prophylactic treatment initiation.

†The triptan medications reported were identified empirically from the most frequently occurring medications dispensed and were selected for inclusion in the propensity score models via stepwise selection

‡Non-delivery indicators include indicators of pre-natal care (e.g., ultrasound and other obstetrical care)

Supplemental Table 4 (online only). Nested case-control analysis: unadjusted and age group and sex-adjusted outcome odds ratios by select comorbidities and concomitant treatments in the 12 months prior to the case or control-defined event date

Outcomes by comorbidity or concomitant treatment*	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Myocardial infarction	182	21,682		
Depression	40 (22.0%)	3,882 (17.9%)	1.29 (0.91, 1.84)	1.44 (1.01, 2.05)
Hypertension	94 (51.6%)	4,592 (21.2%)	3.98 (2.97, 5.33)	2.66 (1.97, 3.60)
Hypercholesterolemia	94 (51.6%)	5,639 (26.0%)	3.04 (2.27, 4.07)	1.90 (1.40, 2.58)
Obesity	29 (15.9%)	1,759 (8.1%)	2.15 (1.44, 3.20)	2.25 (1.50, 3.36)
Asthma	18 (9.9%)	1,828 (8.4%)	1.19 (0.73, 1.94)	1.30 (0.80, 2.13)
Opioids	102 (56.0%)	9,165 (42.3%)	1.74 (1.30, 2.34)	1.66 (1.24, 2.24)
Prescription NSAIDs	61 (33.5%)	6,293 (29.0%)	1.23 (0.91, 1.68)	1.25 (0.91, 1.70)
Hormone replacement therapy	19 (10.4%)	2,156 (9.9%)	1.06 (0.66, 1.70)	0.86 (0.52, 1.42)
Antihyperlipidemics	62 (34.1%)	2,723 (12.6%)	3.60 (2.64, 4.90)	2.10 (1.52, 2.90)
Triptans	97 (53.3%)	12,620 (58.2%)	0.82 (0.61, 1.10)	0.78 (0.58, 1.04)
Ergotamines	1 (0.5%)	190 (0.9%)	0.62 (0.09, 4.48)	0.63 (0.09, 4.52)
Myocardial ischemia	31	4,012		
Depression	6 (19.4%)	734 (18.3%)	1.07 (0.44, 2.62)	1.27 (0.51, 3.13)
Hypertension	19 (61.3%)	829 (20.7%)	6.08 (2.94, 12.57)	4.13 (1.96, 8.73)
Hypercholesterolemia	16 (51.6%)	1,055 (26.3%)	2.99 (1.47, 6.07)	1.83 (0.88, 3.83)
Obesity	3 (9.7%)	311 (7.8%)	1.28 (0.39, 4.22)	1.47 (0.44, 4.93)
Asthma	3 (9.7%)	358 (8.9%)	1.09 (0.33, 3.61)	1.21 (0.36, 4.02)
Opioids	19 (61.3%)	1,704 (42.5%)	2.14 (1.04, 4.43)	2.25 (1.08, 4.68)
Prescription NSAIDs	14 (45.2%)	1,156 (28.8%)	2.03 (1.00, 4.14)	1.99 (0.97, 4.06)
Hormone replacement therapy	4 (12.9%)	406 (10.1%)	1.32 (0.46, 3.78)	1.00 (0.32, 3.06)
Antihyperlipidemics	13 (41.9%)	486 (12.1%)	5.24 (2.55, 10.76)	2.99 (1.40, 6.40)
Triptans	11 (35.5%)	2,294 (57.2%)	0.41 (0.20, 0.86)	0.41 (0.19, 0.86)
Ergotamines	0 (0.0%)	27 (0.7%)	—	—
Unstable angina	84	8,485		
Depression	14 (16.7%)	1,574 (18.6%)	0.88 (0.49, 1.56)	1.04 (0.58, 1.86)
Hypertension	45 (53.6%)	1,768 (20.8%)	4.38 (2.85, 6.75)	2.68 (1.71, 4.19)
Hypercholesterolemia	44 (52.4%)	2,205 (26.0%)	3.13 (2.04, 4.82)	1.76 (1.13, 2.75)
Obesity	11 (13.1%)	696 (8.2%)	1.69 (0.89, 3.19)	1.63 (0.85, 3.10)
Asthma	8 (9.5%)	713 (8.4%)	1.15 (0.55, 2.39)	1.44 (0.69, 3.04)
Opioids	44 (52.4%)	3,493 (41.2%)	1.57 (1.02, 2.42)	1.51 (0.98, 2.33)
Prescription NSAIDs	32 (38.1%)	2,419 (28.5%)	1.54 (0.99, 2.40)	1.63 (1.04, 2.55)
Hormone replacement therapy	10 (11.9%)	860 (10.1%)	1.20 (0.62, 2.33)	1.16 (0.57, 2.37)
Antihyperlipidemics	24 (28.6%)	1,065 (12.6%)	2.79 (1.73, 4.49)	1.28 (0.77, 2.11)
Triptans	40 (47.6%)	4,886 (57.6%)	0.67 (0.44, 1.03)	0.67 (0.43, 1.04)
Ergotamines	0 (0.0%)	62 (0.7%)	—	—
Ischemic stroke	328	39,318		
Depression	93 (28.4%)	6,965 (17.7%)	1.84 (1.44, 2.34)	1.92 (1.51, 2.45)
Hypertension	168 (51.2%)	8,297 (21.1%)	3.93 (3.16, 4.88)	3.21 (2.56, 4.03)
Hypercholesterolemia	150 (45.7%)	10,092 (25.7%)	2.44 (1.96, 3.04)	1.88 (1.49, 2.37)
Obesity	53 (16.2%)	3,198 (8.1%)	2.18 (1.62, 2.93)	2.25 (1.67, 3.02)

Asthma	47 (14.3%)	3,382 (8.6%)	1.78 (1.30, 2.43)	1.88 (1.38, 2.57)
Opioids	205 (62.5%)	16,617 (42.3%)	2.28 (1.82, 2.85)	2.21 (1.77, 2.77)
Prescription NSAIDs	128 (39.0%)	11,470 (29.2%)	1.55 (1.24, 1.94)	1.56 (1.24, 1.95)
Hormone replacement therapy	33 (10.1%)	3,956 (10.1%)	1.00 (0.70, 1.44)	0.79 (0.54, 1.16)
Antihyperlipidemics	94 (28.7%)	4,756 (12.1%)	2.92 (2.29, 3.72)	2.14 (1.66, 2.77)
Triptans	134 (40.9%)	22,945 (58.4%)	0.49 (0.40, 0.61)	0.46 (0.37, 0.58)
Ergotamines	2 (0.6%)	332 (0.8%)	0.72 (0.18, 2.91)	0.69 (0.17, 2.79)
Hemorrhagic stroke	106	12,904		
Depression	32 (30.2%)	2,310 (17.9%)	1.98 (1.31, 3.01)	2.03 (1.33, 3.09)
Hypertension	34 (32.1%)	2,711 (21.0%)	1.78 (1.18, 2.68)	1.47 (0.96, 2.25)
Hypercholesterolemia	42 (39.6%)	3,299 (25.6%)	1.91 (1.29, 2.83)	1.56 (1.02, 2.37)
Obesity	13 (12.3%)	1,028 (8.0%)	1.61 (0.90, 2.90)	1.68 (0.93, 3.01)
Asthma	11 (10.4%)	1,147 (8.9%)	1.19 (0.63, 2.22)	1.24 (0.66, 2.33)
Opioids	61 (57.5%)	5,489 (42.5%)	1.83 (1.24, 2.70)	1.80 (1.22, 2.65)
Prescription NSAIDs	31 (29.2%)	3,771 (29.2%)	1.00 (0.66, 1.52)	0.99 (0.65, 1.51)
Hormone replacement therapy	7 (6.6%)	1,300 (10.1%)	0.63 (0.29, 1.36)	0.48 (0.22, 1.07)
Antihyperlipidemics	23 (21.7%)	1,569 (12.2%)	2.00 (1.26, 3.19)	1.54 (0.94, 2.52)
Triptans	59 (55.7%)	7,494 (58.1%)	0.91 (0.62, 1.33)	0.88 (0.60, 1.29)
Ergotamines	2 (1.9%)	103 (0.8%)	2.39 (0.58, 9.81)	2.29 (0.56, 9.42)
Transient ischemic attack	71	8,562		
Depression	19 (26.8%)	1,527 (17.8%)	1.68 (0.99, 2.86)	1.70 (1.00, 2.88)
Hypertension	33 (46.5%)	1,825 (21.3%)	3.21 (2.01, 5.13)	2.46 (1.51, 4.01)
Hypercholesterolemia	34 (47.9%)	2,175 (25.4%)	2.70 (1.69, 4.31)	1.96 (1.19, 3.20)
Obesity	11 (15.5%)	678 (7.9%)	2.13 (1.12, 4.08)	2.16 (1.13, 4.14)
Asthma	14 (19.7%)	726 (8.5%)	2.65 (1.47, 4.78)	2.63 (1.45, 4.76)
Opioids	39 (54.9%)	3,684 (43.0%)	1.61 (1.01, 2.58)	1.54 (0.96, 2.47)
Prescription NSAIDs	34 (47.9%)	2,525 (29.5%)	2.20 (1.38, 3.51)	2.07 (1.30, 3.32)
Hormone replacement therapy	8 (11.3%)	874 (10.2%)	1.12 (0.53, 2.34)	0.68 (0.32, 1.47)
Antihyperlipidemics	18 (25.4%)	967 (11.3%)	2.67 (1.56, 4.57)	1.80 (1.03, 3.17)
Triptans	30 (42.3%)	5,041 (58.9%)	0.51 (0.32, 0.82)	0.46 (0.29, 0.74)
Ergotamines	0 (0.0%)	69 (0.8%)	—	—
Overall mortality	234	36,974		
Depression	94 (40.2%)	6,578 (17.8%)	3.10 (2.39, 4.03)	3.30 (2.53, 4.30)
Hypertension	116 (49.6%)	7,990 (21.6%)	3.57 (2.76, 4.61)	2.75 (2.10, 3.60)
Hypercholesterolemia	79 (33.8%)	9,562 (25.9%)	1.46 (1.11, 1.92)	1.00 (0.75, 1.32)
Obesity	30 (12.8%)	3,006 (8.1%)	1.66 (1.13, 2.44)	1.73 (1.17, 2.54)
Asthma	34 (14.5%)	3,156 (8.5%)	1.82 (1.26, 2.63)	1.92 (1.33, 2.77)
Opioids	189 (80.8%)	15,658 (42.3%)	5.72 (4.13, 7.92)	5.55 (4.00, 7.69)
Prescription NSAIDs	91 (38.9%)	10,837 (29.3%)	1.53 (1.18, 2.00)	1.55 (1.19, 2.02)
Hormone replacement therapy	19 (8.1%)	3,772 (10.2%)	0.78 (0.49, 1.25)	0.59 (0.36, 0.95)
Antihyperlipidemics	39 (16.7%)	4,619 (12.5%)	1.40 (0.99, 1.98)	0.89 (0.62, 1.27)
Triptans	119 (50.9%)	21,565 (58.3%)	0.74 (0.57, 0.96)	0.69 (0.54, 0.90)
Ergotamines	1 (0.4%)	288 (0.8%)	0.55 (0.08, 3.91)	0.52 (0.07, 3.70)
Cardiovascular and cerebrovascular mortality	27	4,551		
Depression	10 (37.0%)	800 (17.6%)	2.76 (1.26, 6.05)	2.89 (1.31, 6.37)
Hypertension	10 (37.0%)	987 (21.7%)	2.12 (0.97, 4.65)	1.54 (0.68, 3.51)

Hypercholesterolemia	13 (48.1%)	1,169 (25.7%)	2.69 (1.26, 5.73)	1.92 (0.85, 4.33)
Obesity	2 (7.4%)	337 (7.4%)	1.00 (0.24, 4.24)	0.98 (0.23, 4.18)
Asthma	2 (7.4%)	365 (8.0%)	0.92 (0.22, 3.89)	0.94 (0.22, 4.01)
Opioids	20 (74.1%)	1,959 (43.0%)	3.78 (1.60, 8.95)	3.65 (1.54, 8.67)
Prescription NSAIDs	14 (51.9%)	1,318 (29.0%)	2.64 (1.24, 5.64)	2.72 (1.27, 5.81)
Hormone replacement therapy	2 (7.4%)	466 (10.2%)	0.70 (0.17, 2.97)	0.45 (0.10, 2.00)
Antihyperlipidemics	7 (25.9%)	542 (11.9%)	2.59 (1.09, 6.15)	1.66 (0.66, 4.19)
Triptans	10 (37.0%)	2,619 (57.5%)	0.43 (0.20, 0.95)	0.40 (0.18, 0.87)
Ergotamines	0 (0.0%)	33 (0.7%)	—	—
Mortality from trauma	77	9,090		
Depression	39 (50.6%)	1,650 (18.2%)	4.63 (2.95, 7.26)	5.02 (3.19, 7.91)
Hypertension	31 (40.3%)	1,878 (20.7%)	2.59 (1.64, 4.09)	2.64 (1.62, 4.28)
Hypercholesterolemia	23 (29.9%)	2,334 (25.7%)	1.23 (0.76, 2.01)	1.19 (0.71, 1.99)
Obesity	8 (10.4%)	702 (7.7%)	1.39 (0.66, 2.89)	1.44 (0.69, 3.01)
Asthma	15 (19.5%)	754 (8.3%)	2.67 (1.51, 4.72)	2.90 (1.64, 5.14)
Opioids	56 (72.7%)	3,929 (43.2%)	3.50 (2.12, 5.79)	3.62 (2.19, 6.01)
Prescription NSAIDs	25 (32.5%)	2,618 (28.8%)	1.19 (0.74, 1.92)	1.23 (0.76, 1.99)
Hormone replacement therapy	8 (10.4%)	922 (10.1%)	1.03 (0.49, 2.14)	1.48 (0.67, 3.26)
Antihyperlipidemics	12 (15.6%)	1,134 (12.5%)	1.30 (0.70, 2.41)	1.19 (0.62, 2.29)
Triptans	36 (46.8%)	5,224 (57.5%)	0.65 (0.41, 1.02)	0.68 (0.43, 1.08)
Ergotamines	1 (1.3%)	78 (0.9%)	1.52 (0.21, 11.07)	1.53 (0.21, 11.21)
Mortality ascribed to drug overdose	45	5,506		
Depression	24 (53.3%)	972 (17.7%)	5.33 (2.96, 9.61)	5.84 (3.22, 10.60)
Hypertension	23 (51.1%)	1,189 (21.6%)	3.80 (2.11, 6.83)	4.00 (2.14, 7.48)
Hypercholesterolemia	14 (31.1%)	1,396 (25.4%)	1.33 (0.71, 2.51)	1.24 (0.63, 2.43)
Obesity	6 (13.3%)	444 (8.1%)	1.75 (0.74, 4.17)	1.83 (0.77, 4.37)
Asthma	10 (22.2%)	500 (9.1%)	2.86 (1.41, 5.81)	3.03 (1.48, 6.18)
Opioids	38 (84.4%)	2,306 (41.9%)	7.53 (3.36, 16.90)	7.50 (3.34, 16.86)
Prescription NSAIDs	20 (44.4%)	1,630 (29.6%)	1.90 (1.05, 3.43)	1.95 (1.08, 3.53)
Hormone replacement therapy	3 (6.7%)	553 (10.0%)	0.64 (0.20, 2.07)	0.76 (0.23, 2.59)
Antihyperlipidemics	8 (17.8%)	669 (12.2%)	1.56 (0.72, 3.37)	1.44 (0.64, 3.24)
Triptans	19 (42.2%)	3,183 (57.8%)	0.53 (0.29, 0.97)	0.55 (0.30, 0.99)
Ergotamines	0 (0.0%)	52 (0.9%)	—	—

Abbreviations: OR, odds ratio; CI, confidence interval; NSAIDs, nonsteroidal antiinflammatory drugs

*Patients may have multiple comorbidities or concomitant treatments prior to the case or control-defined event date. The odds ratios compared the presence versus no presence of the specified comorbidity or concomitant treatment in the 12 months prior to the case or control-defined event date.

Supplemental Table 5 (online only). Nested case-control analysis: unadjusted and adjusted outcome odds ratios among cases and controls with topiramate use in the 3 months prior to the case or control-defined event date

Outcome*	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)^{†,‡}
Myocardial infarction	N = 161	N = 20,528		
Topiramate	21	2,417	1.04 (0.66, 1.64)	1.09 (0.65, 1.81)
Myocardial ischemia[§]	26	3,787		
Topiramate	7	469	2.20 (0.94, 5.14)	2.52 (0.96, 6.65)
Unstable angina[¶]	70	7,981		
Topiramate	10	974	1.04 (0.54, 2.02)	0.92 (0.41, 2.07)
Ischemic stroke	294	37,162		
Topiramate	56	4,427	1.62 (1.22, 2.17)	1.36 (0.98, 1.90)
Hemorrhagic stroke	94	12,193		
Topiramate	11	1,443	0.92 (0.49, 1.72)	0.69 (0.33, 1.41)
Transient ischemic attack	63	8,156		
Topiramate	18	972	2.65 (1.55, 4.55)	2.08 (1.11, 3.91)
Overall mortality	210	34,836		
Topiramate	18	4,225	0.65 (0.40, 1.05)	0.44 (0.25, 0.78)
Cardiovascular and cerebrovascular mortality	23	4,254		
Topiramate	8	1,044	0.89 (0.43, 1.86)	0.74 (0.32, 1.69)
Mortality ascribed to trauma	74	8,552		
Topiramate	5	633	0.96 (0.38, 2.45)	0.39 (0.12, 1.24)
Mortality ascribed to drug overdose	41	5,181		
Topiramate	3	511	0.99 (0.30, 3.29)	0.37 (0.08, 1.82)

Abbreviations: OR, odds ratio; CI, confidence interval

*Patients may have been exposed to multiple prophylactic medications prior to the case or control-defined event date. The odds ratios compared any use of topiramate to no use of topiramate in the 3 months prior to the case or control-defined event date.

[†]Except where noted, regression models comparing topiramate exposure to non-exposure were adjusted for age group, sex, and presence of hypertension, depression, other anticonvulsants, beta blockers, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, calcium channel blockers, antihypertensives, and other prophylactic treatments prior to the topiramate dispensing.

[‡]Adjustment for age group in the regression models was done using the following categories (in years): 18-24, 25-34, 35-44, 45-54, 55-65, >65. Due to the small number of cases within certain age strata, age groups were collapsed for select outcome regression models as follows: myocardial infarction, unstable angina, transient ischemic attack: 18-34, 35-44, 45-54, 55-65, >65; myocardial ischemia: 18-44, 45-54, 55-65, >65.

[§]Due to sample size constraints, the regression model was adjusted for age group, sex, and presence of hypertension, depression, other anticonvulsants, cardiovascular treatments (consisting of beta blockers, calcium channel blockers, antihypertensives), antidepressants (consisting of tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors) and other prophylactic treatments prior to the topiramate dispensing.

[¶]The regression model was adjusted for age group and sex due to sample size constraints.