Supplemental Digital Content A – Procedural codes to define study population

|  |  |
| --- | --- |
| Procedure | CCI codes |
| ORTHOPEDIC |  |
| Total hip replacement | 1.VA.53.LA-PN ; 1.VA.53.PN-PN |
| Total knee replacement | 1.VG.53 |
| VASCULAR |  |
| Carotid endarterectomy | 1.JE.57 without 1.IJ.76 on the same date (exclude concurrent CABG surgery) |
| Endovascular Abdominal aortic aneurysm repair | 1.KA.80.GQ-NRN or  1.KA.50.GS-BD or  1.KA.50.LA-BD or  1.KE.50.GQ-OA or  1.KE.51.GQ-GE  [must have ICD-10 code I71.4 on the same admission] |
| Open Abdominal aortic aneurysm repair | 1.KA.80.LA-XXN or  1.KA.76.NB-XXN or  1.KA.76.MZ-XXN  [must have ICD-10 code I71.4 on the same admission] |
| Peripheral arterial bypass surgery | 1.KG.76 ; 1.JM.76.MI ; 1.KT.76 ; 1.KG.80 or CCI code 1.KA.76 without ICD-10 codes I71.3 or I71.4 or I71.9 on the same admission. |
| UROLOGIC |  |
| Partial or total nephrectomy | 1.PC.87 ; 1.PC.89 ; 1.PC.91 |
| Total cystectomy | 1.PM.89 ; 1.PM.90 ; 1.PM.91 ; 1.PM.92 |
| INTRAPERITONEAL | DAD |
| Large bowel and rectal surgery | 1.NM.87 (all except 1.NM.87.BA) or 1.NM.89 ; 1.NM.91 ; 1.NQ.89 ; 1.NQ.90 or 1.NQ.87 (all except 1.NQ.87.BA) |
| Partial liver resection | 1.OA.87 |
| Pancreaticoduodenectomy | 1.OK.87 ; 1.OK.89 ; 1.OK.91 |
| Gastrectomy or esophagectomy | 1.NF.87 ; 1.NF.89 ; 1.NF.90 ; 1.NF.91 ; 1.NF.92 ; 1.NA.88 ; 1.NA.89 ; 1.NA.90 ; 1.NA.91 ; 1.NA.92 ; 1.NA.87 |
| THORACIC |  |
| Pneumonectomy and lobectomy | 1.GR.89 ; 1.GR.91 ; 1.GT.89 ; 1.GT.91 ; 1.GT.87 |

Supplemental Digital Content B - List of high risk centrally acting drugs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Benzodiazepines** | **Antipsychotics** | **Anticonvulsants** | **Opioids** | **Anti-depressants** |
| Alprazolam | Aripiprazole | Topiramate | Alfentanil | Amitriptyline |
| Bromazepam | Asenapine | Carbamazepine | Codeine | Amoxipine |
| Chloridiazepoxide | Chlormezanone | Ethosuximide | Fentanyl | Bupropion |
| Clobazam | Chlorpromazine | Felbamate | Hydromorphone | Citalopram |
| Clonazepam | Chlorprothixene | Fosphenytoin | Meperidine | Clomipramine |
| Clorazepate | Clozapine | Gabapentin | Methadone | Desipramine |
| Diazepam | Flupentixol | Lacosamide | Morphine | Desvenlafaxine |
| Flurazepam | Fluphenazine | Lamotrigine | Oxycodone | Doxepin |
| Lorazepam | Fluspirilene | Levetiracetem | Sufentanil | Duloxetine |
| Midazolam | Haloperidol | Mephenytoin |  | Escitalopram |
| Nitrazepam | Loxapine | Methsuximide |  | Fluoxitine |
| Oxazepam | Mesoridazine | Oxcarbazepine |  | Fluvoxamine |
| Temazepam | Methotrimeprazine | Parmethadione |  | Imipramine |
| Triazolam | Olanzapine | Phensuximide |  | Maprotilene |
|  | Paliperidone | Phenytoin |  | Mirtazepine |
|  | Periciazine | Pregabalin |  | Nortiptyline |
|  | Perphenazine | Steripentol |  | Paroxetine |
|  | Pimozide | Trimethdione |  | Sertraline |
|  | Pipotiazine | Valproic acid |  | Trazodone |
|  | Prochlorperazine |  |  | Trimipramine |
|  | Quetiapine |  |  | Venlafaxine |
|  | Risperidone |  |  |  |
|  | Thiorizaine |  |  |  |
|  | Thiothixene |  |  |  |
|  | Trifluoperazine |  |  |  |
|  | Ziprasidone |  |  |  |
|  | Zuclopenthixol |  |  |  |

Supplemental Digital Content C – List of all sensitivity analyses and results

|  |  |  |
| --- | --- | --- |
| **Description of analysis** | **Adjusted HR\*** | **95% CI** |
| **Primary exposure** |  |  |
| >= 5 drugs in 90 days before surgery | 1.21 | 1.14-1.27 |
| **Change in lookback period to count number of drugs** |  |  |
| 180 days | 1.23 | 1.14-1.32 |
| 30 days | 1.07 | 1.01-1.14 |
| **Change in comorbidity adjustment** |  |  |
| ADG Score | 1.12 | 1.05-1.20 |
| **Change in procedural risk adjustment** |  |  |
| Stratification by surgery type | 1.20 | 1.14-1.27 |
| **Effect modification by frailty** |  |  |
| >= 5 drugs in 90 days before surgery-not frail | 1.30 | 1.21-1.41 |
| >= 5 drugs in 90 days before surgery-frail | 0.92 | 0.79-1.08 |
| **Effect modification by comorbidity burden** |  |  |
| >= 5 drugs in 90 days before surgery-0 comorbidities | 1.30 | 1.15-1.47 |
| >= 5 drugs in 90 days before surgery-1-2 comorbidities | 1.14 | 1.02-1.26 |
| >= 5 drugs in 90 days before surgery->=3 comorbidities | 0.96 | 0.82-1.12 |
|  |  |  |
| **Change in polypharmacy definition** |  |  |
| Linear predictor (i.e., increase in risk for each extra drug) | 1.01 | 1.01-1.01 |
| High risk centrally acting drug count (0=reference) |  |  |
| 1 | 1.08 | 1.02-1.14 |
| 2 | 1.23 | 1.14-1.32 |
| >=3 | 1.21 | 1.09-1.35 |
| **Effect modification by frailty** |  |  |
| High risk centrally acting drug count=1-not frail | 1.13 | 1.06-1.21 |
| High risk centrally acting drug count=2-not frail | 1.36 | 1.25-1.48 |
| High risk centrally acting drug count=>=3-not frail | 1.27 | 1.11-1.45 |
| High risk centrally acting drug count=1-frail | 0.88 | 0.77-0.99 |
| High risk centrally acting drug count=2-frail | 0.89 | 0.77-1.03 |
| High risk centrally acting drug count=>=3-frail | 1.02 | 0.85-1.22 |
| **Effect modification by comorbidity burden** |  |  |
| High risk centrally acting drug count=1-0 comorbidities | 1.09 | 0.97-1.24 |
| High risk centrally acting drug count=2-0 comorbidities | 1.49 | 1.26-1.76 |
| High risk centrally acting drug count>=3-0 comorbidities | 1.40 | 1.06-1.84 |
| High risk centrally acting drug count=1-1-2 comorbidities | 1.08 | 0.99-1.18 |
| High risk centrally acting drug count=2-1-2 comorbidities | 1.29 | 1.15-1.44 |
| High risk centrally acting drug count>=3-1-2 comorbidities | 1.18 | 0.99-1.41 |
| High risk centrally acting drug count=1->=3 comorbidities | 1.04 | 0.94-1.19 |
| High risk centrally acting drug count=2->=3 comorbidities | 1.05 | 0.93-1.19 |
| High risk centrally acting drug count>=3->=3 comorbidities | 1.15 | 0.99-1.35 |
| \*HR:hazard ratio denotes relative strength of association between exposure and 90-day survival. All analyses adjusted for covariates listed in manuscript Table 2 unless otherwise specified; ADG: Johns Hopkins Adjusted Diagnosis Groups; CI-confidence interval | | |