Supplementary Online Content

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eTable 1. National Formulary Drug Classes Extracted From PBM Database

Drug Class	VA Class Description	Representative Drugs
BL 100/110	Anticoagulants	Heparin, warfarin, enoxaparin
BL 700/117	Platelet Aggregation Inhibitors	Clopidogrel
CN 103	Non-Opioid Analgesics	Aspirin
CV 050	Digitalis Glycosides	Digoxin
CV 100	Beta Blockers	Atenolol, metoprolol, carvedilol
CV 150	Alpha Blockers	Terazosin, prazosin
CV 200	Calcium Channel Blockers	Amlodipine, nifedipine, diltiazem, verapamil
CV 250	Antianginals	Isosorbide, nitroglycerin
CV 300	Antiarrhythmics	Amiodarone, flecanide
CV 350	Antilipemic Agents	Statins, ezetimibe, cholystyramine, colestipol, gemfibrozil
CV 400	Antihypertensive combinations	Beta blocker, ACE-I diuretic combinations
CV 490	Other Antihypertensives	Clonidine, hydralazine, minoxidil
CV 701	Thiazides/Related Diuretics	HCTZ, metolazone
CV 702	Loop Diuretics	furosemide
CV 704	Potassium sparing, combination diuretics	HCTZ/triamterene
CV 709	Other Diuretics	HCTZ/Losartan
CV 800	ACE Inhibitors	Fosinopril, lisinopril, enalapril
CV 805	Angiotensin II Inhibitors	Losartan, valsartan
HS 501	Insulin	NPH, novolin, aspartate
HS 502	Oral hypoglycemic agents	Glipizide, glyburide, metformin, rosiglitazone
RE 101	Antinflammatories, inhalation	flunisolide
RE 102	Bronchodilators, inhalation, sympathomimetic	Albuterol, formoterol
RE 105	Bronchodilators, cholinergic	Ipratropium

RE 109	Antiasthma, other	Albuterol/ipratropium

eTable 2. *ICD-9* Variables From the OPC-PTF Database

Variable	ICD-9 codes used
Ischemic Heart Disease	410, 411, 412, 413, 414, V4581, V4582
Cardiac Conduction Disorders	426.0, 426.10, 426.11, 426.11, 426.12, 426.13, 426.2, 426.3, 426.4, 426.5, 426.51, 426.52, 426.53, 426.54, 426.6, 426.7, 426.81, 426.89, 426.9, 427.81, V450, V4500, V4501, V4502, V4509, V533, V5331, V5332, V5339, V5400, V5401, V5402, V5409
Cardiac Dysrhythmias	427.0, 427.1, 427.2, 427.31, 427.32, 427.41, 427.42, 427.5, 427.60, 427.61, 427.69, 427.81, 427.89, 427.9, 7850, 7851, V4502
Hypertension	401.0, 401.1, 401.9, 402.0, 402.01, 402.1, 402.11, 402.9, 402.91, 403.0, 403.00, 403.01, 403.1, 403.10, 403.11, 403.9, 403.90, 403.91, 404.0, 404.01, 404.02, 404.03, 404.1, 404.10, 404.11, 404.12, 404.13, 404.9, 404.90, 404.91, 404.92, 404.93, 404.01, 405.11, 405.19, 405.91, 405.99, 437.2
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 416.9, 425.1, 425.4, 425.5, 425.7, 425.8, 425.9, 428.0, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9, 429.3, V1259
Peripheral Vascular Disease	440, 4410, 44100, 44101, 44102, 44103, 4411, 4412, 4413, 4414, 4415, 4416 , 4417, 4419, 4420, 4421, 4422, 4423, 4428, 44282, 44283, 44284, 44289, 4429, 4439, 44321, 44322, 44323, 44324, 44329, 444, 445, 5570, 5571, 5579
Asthma	493
Renal Failure	585.00, 585.30, 585.40, 585.50, 585.60, 585.90, V420, V451, V560, V561, V562, V5631, V5632, V568
Hepatitis	0702 , 07020, 07021, 07022, 07023, 0703 , 07030, 07031, 07032, 07033, 0704 , 07041, 07042, 07043, 07044, 07049, 0705 , 07051, 07052, 07053, 07054, 07059, 0706 , 07070 07071, 0709 , 57140, 57141, 57149, 5731 , 5732 , 5733

eTable 3. Coding of the Revised Cardiac Risk Index

	Data sources	**Variables Used**
High risk surgery	VASQIP	VASQIP CPT/specialty codes for intrathoracic, intraperitoneal or suprainguinal vascular surgery
Ischemic heart disease	VASQIP/PBM (OPC-PTF)*	VASQIP Prior MI or Angina or PBM Anti-anginal Drugs (CV250) (or ICD9 Ischemic Heart Disease grouping)*
Congestive heart failure	VASQIP/OPC-PTF	VASQIP CHF or OPC/-PTF ICD9 Congestive Heart Failure grouping
Cerebrovascular disease	VASQIP	VASQIP CVA with neurologic deficit or CVA with no neurologic deficit or hemiplegia or history TIA
Diabetes (Primary)	VASQIP/PBM	VASQIP Insulin Rx or Outpatient PBM insulin (HS501)
Diabetes (Secondary)	VASQIP/PBM	VASQIP Diabetes oral agents or insulin Rx or Outpatient PBM Insulin (HS501) or Oral agents (HS 502) or Preoperative Inpatient Insulin (HS501)
Renal insufficiency	VASQIP/OPC-PTF	VASQIP Preoperative serum creatinine > 2.0 mg/dl or preoperative dialysis or preoperative acute renal failure or OPC-PTF ICD9 Chronic Renal Failure grouping

eTable 4. Variables Used in the Propensity Model

Variable	**Data source**
DEMOGRAPHICS	
Age	VASQIP
Race	VASQIP
Gender	VASQIP
Body Mass Index	VASQIP
Veterans Integrated Service Network	VASQIP
Fiscal Year	VASQIP
PREOPERATIVE RISK VARIABLES	
CARDIOVASCULAR	
Hx Angina within 30 days preop	VASQIP
Hx CHF within 30 days preop	VASQIP
Previous PTCA/PCI	VASQIP
Previous Cardiac Surgery	VASQIP
Hypertension on medication	VASQIP
Revascularization/amputation for PVD	VASQIP
Rest Pain/Gangrene 30 days preop	VASQIP
Peripheral Vascular Disease	PTF/OPC
Conduction disorders	PTF/OPC
Dysrhythmias	PTF/OPC
GENERAL STATUS VARIABLES	
ASA Classification	VASQIP
Alcohol Use > 2 drinks/day	VASQIP
Functional health status 30 days preop	VASQIP
Do not resuscitate status	VASQIP
Current Smoker within 1 yr preop	VASQIP

Variable	Data source
Preoperative sepsis within 48 hrs	VASQIP
HEPATOBILIARY	
Hepatitis	PTF/OPC
NUTRITIONAL/IMMUNE/OTHER	
Disseminated cancer	VASQIP
Wound infection	VASQIP
Steroid use	VASQIP
Weight loss > 10%	VASQIP
Bleeding disorder	VASQIP
Radiotherapy for cancer	VASQIP
PULMONARY	
Asthma	PTF/OPC
COPD	VASQIP/PTF/OPC
CENTRAL NERVOUS SYSTEM	
Impaired sensorium	VASQIP
REVISED CARDIAC RISK INDEX	
Congestive Heart Failure	VASQIP/PTF/OPC
Cerebrovascular disease	VASQIP/PTF/OPC
Diabetes	VASQIP/PTF/OPC
Ischemic Heart Disease	VASQIP/PTF/OPC
High Risk Surgery	VASQIP
Renal Insufficiency	VASQIP/PTF/OPC
PREOPERATIVE MEDICATIONS	
Diuretics	PBM

Variable	Data source
ACE-I/ARBs	PBM
Calcium Entry Blocker-dihydropyridine	PBM
Calcium Entry Blocker-nondihydropyridine	PBM
Clonidine	PBM
Other Antihypertensives	PBM
Digoxin/Anti-arrhythmics	PBM
NonStatin Antilipemic Agent	PBM
Atenolol	PBM
Metoprolol Tartrate	PBM
Metoprolol Succinate	PBM
Carvedilol	PBM
Other Beta Blocker	PBM
Rosiglitazone	PBM
Anticoagulant/antiplatelet agents	PBM
Bronchodilators	PBM
PREOPERATIVE LABORATORY DATA (serum or plasma)	
Albumin	VASQIP
Alkaline Phosphatase	VASQIP
Total Bilirubin	VASQIP
Blood urea nitrogen	VASQIP
Hematocrit	VASQIP
Platelet count	VASQIP
International Normal Ratio	VASQIP
Partial thromboplastin time	VASQIP
SGOT	VASQIP
Sodium	VASQIP

Variable	Data source
White blood cell count	VASQIP
SURGICAL DETAILS	
Surgical Specialty Grouping	VASQIP
Work Portion of Medicare RVU	VASQIP
Emergency procedure	VASQIP
Laparoscopic procedure	VASQIP
Endovascular procedure	VASQIP
Duration of Surgery	VASQIP
Principal Anesthesia Technique	VASQIP
Wound classification	VASQIP
Number of units RBC's transfused	VASQIP

Abbreviations: OPC, Outpatient Care Datafile; PBM, Pharmacy Benefits Management Datafile; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; PTF, Patient Treatment File Datafile; RBCs Packed or whole red blood cell units; RVU Resource Based Relative Value System; VASQIP, Veterans Affairs Surgical Quality Improvement Program

eTable 5. Standardized Differences for Propensity Model Variables

Variable	Before Matching, % N= 180,478	After Matching, % N= 96,486
DEMOGRAPHICS		
Age	32.0	2.1
Race		
-White	8.2	0.06
-Black	11.0	0.6
-Other	0.9	0.2
-Unknown	0.2	0.4
Gender	7.7	0.1
Body Mass Index	20.2	0.6
Fiscal Year		
-2006	5.7	0.4
-2007	2.4	0.08
-2008	1.2	0.4
-2009	3.0	0.3
-2010	3.3	0.3
PREOPERATIVE RISK VARIABLES		
CARDIOVASCULAR		
VASQIP		
Hx Angina within 30 days preop	8.6	0.2
Hx CHF within 30 days preop	6.8	0.2
Previous PTCA/PCI	29.4	1.1
Previous Cardiac Surgery	31.9	1.5
Hypertension on medication	39.1	2.3
Revascularization/amputation PVD	19.8	0.4
Rest pain/gangrene 30 d preop	14.5	0.1

Variable	Before Matching, % N= 180,478	After Matching, % N= 96,486
ICD-9 (PTF/OPC)		
Peripheral Vascular Disease	28.8	0.04
Conduction disorders	13.2	0.3
Dysrhythmias	12.8	0.7
GENERAL VARIABLES		
ASA Classification		
-1	12.0	1.0
-2	24.9	0.4
-3	16.3	0.5
-4	9.1	0.1
Alcohol Use > 2 drinks/day	12.0	0.2
Functional health status	0.5	1.2
Do not resuscitate status	1.0	0.5
Current Smoker within 1 yr preop	12.9	0.9
Preoperative sepsis within 48 hrs	5.1	0.4
HEPATOBILIARY		
Hepatitis	20.5	0.8
NUTRITIONAL/IMMUNE/OTHER		
Disseminated cancer	9.2	0.3
Wound infection	8.0	0.6
Steroid use 30 d preop	1.0	0.1
Weight loss > 10%	10.2	0.1
Bleeding disorder	7.2	0.8
Radiotherapy for cancer	8.3	0.3

Variable	Before Matching, % N= 180,478	After Matching, % N= 96,486
PULMONARY		
COPD	6.8	0.1
Asthma	3.7	0.3
CENTRAL NERVOUS SYSTEM		
Impaired sensorium	1.4	0.1
REVISED CARDIAC RISK INDEX VARIABLES		
Congestive Heart Failure	21.0	0.1
Cerebrovascular disease	19.5	0.03
Diabetes	36.5	0.3
Ischemic Heart Disease	49.5	1.2
High Risk Surgery	38.3	1.0
Renal Insufficiency	6.7	0.4
PREOPERATIVE LABS		
Serum Albumin	5.5	0.5
Alkaline Phosphatase	7.7	1.1
Total Bilirubin	10.2	0.4
Blood urea nitrogen	20.4	0.1
Hematocrit	5.3	0.1
Platelet count	10.2	0.3
Prothrombin time	1.1	0.9
Partial thromboplastin time	4.1	0.4
Serum glutamic oxaloacetate	12.1	1.4
Serum Sodium	4.8	0.5
White blood cell count	2.5	0.1

Variable	Before Matching, % N= 180,478	After Matching, % N= 96,486
PREOPERATIVE MEDICATIONS		
Diuretics	24.0	0.5
ACE-I/ARBs	45.6	2.2
Calcium Entry Blocker-dihydropyridine	16.5	0.3
Calcium Entry Blocker-nondihydropyridine	2.9	2.0
Clonidine	1.6	0.9
Other Antihypertensives	6.3	1.9
Digoxin/Anti-arrhythmics	6.1	1.4
NonStatin Antilipemic Agent	8.2	0.01
Atenolol	14.8	1.0
Metoprolol Tartrate	30.4	0.2
Metoprolol Succinate	14.7	1.0
Carvedilol	12.3	0.4
Other Beta Blocker	0.2	1.0
Rosiglitazone	11.0	0.2
Anticoagulant/antiplatelet agents	24.6	9.2
Bronchodilators	6.7	0.5
SURGICAL DETAILS		
Surgery type		
-General	40.3	0.1
-Neurosurgery	5.3	0.4
-Orthopedics	21.0	0.3
-ENT	6.1	0.3
-Thoracic	4.2	0.3
-Urology	6.4	1.0
-Vascular	30.2	0.9

Variable	Before Matching, % N= 180,478	After Matching, % N= 96,486
Work Portion Medicare RVU	8.5	1.0
Emergency procedure	13.7	0.3
Laparoscopic procedure	14.1	0.5
Endovascular procedure	13.0	0.4
Duration of Surgery	11.6	0.2
Principal Anesthetic Technique		
-General	16.1	0.1
-Spinal	13.6	0.3
-Other	7.8	0.4
Wound classification	23.0	1.9
Red blood units transfused	6.7	0.9

eTable 6. Drug Exposure Covariate Interaction Sensitivity Analysis

	Death	95% CI		*P* Value	Any Complication	95% CI		*P* Value	Cardiac	95% CI		*P* Value
Surgery												
-Vascular	0.80	0.66	0.91	.59	0.80	0.73	0.89	.25	0.70	0.54	0.93	.40
-General	0.92	0.79	1.09		0.85	0.79	0.92		0.86	0.68	1.08	
-Orthopedic	0.74	0.62	0.88		0.83	0.76	0.91		0.75	0.57	1.00	
-Other	0.80	0.67	0.94		0.79	0.72	0.86		0.58	0.45	0.76	
RCRI vars												
0	0.81	0.72	0.90	.94	0.84	0.79	0.90	.46	0.70	0.59	0.84	.95
1	0.76	0.54	1.09		0.82	0.72	0.94		0.80	0.46	1.40	
2	0.94	0.73	1.22		0.84	0.76	0.93		0.81	0.57	1.15	
3	0.88	0.70	1.12		0.79	0.70	0.89		0.72	0.52	0.99	
4 or more	1.00	0.76	1.32		0.91	0.78	1.05		1.06	0.72	1.55	
Age												
> 75	0.85	0.75	0.97	.21	0.83	0.79	0.88	.57	0.88	0.72	1.08	.009
< 75	0.87	0.77	0.98		0.84	0.78	0.91		0.66	0.56	0.79	
IHD												
Yes	0.81	0.73	0.91	.054	0.76	0.72	0.81	.007	0.66	0.57	0.78	.15
No	0.81	0.71	0.93		0.87	0.82	0.93		0.87	0.68	1.10	

Diabetes												
Yes	0.76	0.66	0.87	.20	0.78	0.73	0.84	.045	0.67	0.55	Yes	.76
No	0.86	0.77	0.96		0.85	0.80	0.90		0.77	0.65	No	.86
CHF											CHF	
Yes	0.76	0.66	0.89	.37	0.76	0.70	0.83	.42	0.70	0.56	Yes	.76
No	0.85	0.76	0.94		0.84	0.80	0.88		0.74	0.63	No	.85
CVD											CVD	
Yes	0.77	0.65	0.91	.85	0.83	0.75	0.91	.57	0.71	0.55	Yes	.77
No	0.84	0.75	0.93		0.82	0.78	0.86		0.73	0.63	No	.84
High Risk Surgery											High Risk Surgery	
Yes	0.84	0.73	0.96	.17	0.80	0.75	0.85	.024	0.76	0.63	Yes	.84
No	0.81	0.72	0.90		0.84	0.79	0.90		0.70	0.59	No	.81
Renal											Renal	
Yes	0.88	0.72	1.07	.80	0.87	0.76	0.99	.67	0.71	0.52	Yes	.88
No	0.80	0.73	0.88		0.81	0.78	0.85		0.73	0.63	No	.80
Overall	0.90	0.85	0.94		0.89	0.87	0.92		0.84	0.78	Overall	.90

eTable 7. Logistic Regression Intensity Dosing and Patterns of Use Sensitivity Analysis

	Death (N/%)	OR (95% CI)	*P* Value	Cardiac (N/%)	OR (95% CI)	*P* Value	CNS (N/%)	OR (95% CI)	*P* Value
Rx Admit	180048 (2.2)			179594 (0.9)			179801 (0.4)		
None	2.3	1		0.9	1		0.3	1	
Low	2.4	1.02 (0.89,1.16)	.77	1	0.99 (0.81,1.21)	.9	0.4	1.05 (0.77,1.43)	.76
Medium	1.9	0.81 (0.75, 0.89)	<.0001	1	0.89 (0.79, 1.01)	.08	0.4	0.91 (0.74,1.10)	.3
High	2	0.80 (0.71,0.91)	.0006	1	0.92 (0.78, 1.09)	.34	0.4	0.94 (0.71,1.23)	.6
90-Day Use	180048 (2.2)			179594 (0.9)			179801 (0.4)		
None	2.3	1		0.8	1		0.3	1	
Low	2.4	1.03 (0.91,1.16)	.68	0.9	0.91 (0.75,1.1)	.3	0.4	0.97 (0.72,1.31)	.9
Medium	2	0.84 (0.77,0.91)	<.0001	1	0.91 (0.80,1.03)	.1	0.4	0.94 (0.77,1.14)	.5
High	2	0.79 (0.71,0.89)	.0001	1.2	0.96 (0.82,1.12)	.6	0.4	0.86 (0.66,1.12)	.3

	Death (N/%)	OR (95% CI)	*P* Value	Cardiac (N/%)	OR (95% CI)	*P* Value	CNS (N/%)	OR (95% CI)	*P* Value
Indeterminate Pattern of Use	180048 (2.2)			179594 (0.9)			179801 (0.4)		
Never	2.3	1		0.8	1		0.3	1	
New	2.4	0.87 (0.78,0.98)	.017	1.4	1.27 (1.09,1.49)	.002	0.6	1.43 (1.12,1.81)	.004
Withdraw	2.4	0.91 (0.84, 1.0)	.04	1.1	1.01 (0.89, 1.16)	.8	0.5	1.19 (0.97,1.46)	.1
Stayed On	1.6	0.68 (0.61,0.76)	<.0001	0.9	0.94 (0.81,1.10)	.4	0.3	0.86 (0.67,1.10)	.2
Concordant Pattern of Use	156331 (2.2)			155980 (0.9%)			156139 (0.3)		
Never	2.3	1		0.8	1		0.3	1	
New	1.9	0.74 (0.63,0.86)	.0001	0.9	0.89 (0.7,1.11)	.3	0.4	1.08 (0.78,1.50)	.7
Withdraw	2.6	1.00 (0.90,1.10)	.96	1.2	1.11 (0.95,1.29)	.2	0.4	1.11 (0.86,1.44)	.4
Stayed On	1.6	0.67 (0.60,0.75)	<.0001	0.9	0.92 (0.79,1.08)	.3	0.3	0.85 (0.66,1.10)	.2

	Thrombosis (N/%)	OR (95% CI)	*P* Value	Infections (N/%)	OR (95% CI)	*P* Value	Respiratory (N/%)	OR (95% CI)	*P* Value
Rx Admit	179767 (1.3)			179571 (3.8)			178269 (4.6)		
None	1.3	1		3.9	1		4.7	1	
Low	1.3	0.98 (0.82,1.17)	.8	3.6	0.91 (0.81,1.01)	.09	4.4	0.95 (0.86,1.05)	.4
Medium	1.2	0.97 (0.87,1.08)	.6	3.3	0.85 (0.79,0.91)	<.001	4.4	0.93 (0.87,0.99)	.02
High	1.3	0.96 (0.82,1.12)	.6	3.6	0.93 (0.85,1.03)	.16	4.6	0.98 (0.90,1.07)	.7
90-Day Use	179767 (1.3)			179571 (3.8)			178266 (4.6)		
None	1.2	1		3.9	1		4.6	1	
Low	1.3	1.02 (0.87,1.2)	.8	3.8	0.98 (0.89,1.08)	.7	4.5	0.97 (0.88,1.07)	.6
Medium	1.3	0.98 (0.88,1.08)	.7	3.6	0.92 (0.86,0.98)	.014	4.5	0.96 (0.91,1.02)	.2
High	1.3	0.96 (0.83,1.11)	.6	3.7	0.98 (0.90,1.07)	.67	4.7	1.00 (0.92,1.09)	.9

	Thrombosis (N/%)	OR (95% CI)	*P* Value	Infections (N/%)	OR (95% CI)	*P* Value	Respiratory (N/%)	OR (95% CI)	*P* Value
Indeterminate Pattern of Use	179767 (1.3)			179571 (3.8)			178266 (4.6)		
Never	1.2	1		3.9	1		4.5	1	
New	1.6	1.12 (0.97,1.29)	.1	4.2	1.08 (0.99,1.18)	.09	5.3	1.08 (0.99,1.17)	.08
Withdraw	1.3	1.07 (0.95,1.2)	.3	4	0.92 (0.86,0.98)	.02	5.4	1.03 (0.97,1.1)	.4
Stayed On	1.2	0.90 (0.79,1.03)	.1	2.7	0.84 (0.77,0.92)	<.0001	3.3	0.83 (0.77,0.91)	<.0001
Concordant Pattern of Use	156097 (1.2)			155930 (3.7)			154887 (4.4)		
Never	1.2	1		3.9	1		4.5	1	
New	1.4	0.99 (0.83,1.19)	>.99	3.2	0.97 (0.86,1.1)	.7	3.9	0.94 (0.83,1.05)	.3
Withdraw	1.3	1.02 (0.88,1.17)	.8	4.2	0.94 (0.86,1.02)	.1	5.8	1.09 (1.01,1.17)	.03
Stayed On	1.2	0.88 (0.77,1.01)	.07	2.7	0.85 (0.78,0.93)	.0003	3.3	0.82 (0.75,0.89)	<.0001

	Renal (N/%)	OR (95% CI)	*P* Value	Any Complication (N/%)	OR (95% CI)	*P* Value
Rx Admit	179732 (1.1)			176892 (8.5)		
None	1	1		8.6	1	
Low	1.1	0.97 (0.81,1.17)	.8	8.3	0.95 (0.88,1.02)	.2
Medium	1.2	1.03 (0.92,1.15)	.6	8.2	0.91 (0.87,0.96)	.0002
High	1.5	1.18 (1.02,1.37)	.03	8.6	0.96 (0.90,1.03)	.3
90-Day Use	179732 (1.1)			176892 (8.5)		
None	1	1		8.4	1	
Low	1.1	0.93 (0.78,1.11)	.4	8.6	0.99 (0.92,1.06)	.7
Medium	1.2	0.98 (0.87,1.09)	.7	8.4	0.95 (0.91,1.00)	.046
High	1.5	1.15 (1.0,1.33)	.054	8.8	0.99 (0.93,1.06)	.8

	Renal (N/%)	OR (95% CI)	*P* Value	Any Complication (N/%)	OR (95% CI)	*P* Value
Indeterminate Pattern of Use	179732 (1.1)			176892 (8.5)		
Never	1	1		8.3	1	
New	1.2	0.87 (0.74,1.02)	.08	9.8	1.09 (1.02,1.16)	.007
Withdraw	1.4	1.05 (0.93,1.17)	.5	9.5	1.01 (0.96,1.06)	.6
Stayed On	1.1	0.97 (0.85,1.12)	.7	6.8	0.85 (0.80,0.91)	<.0001
Concordant Pattern of Use	156053 (1.1)			153755 (8.2)		
Never	1	1		8.3	1	
New	0.9	0.77 (0.62,0.95)	.018	7.8	0.94 (0.86,1.02)	.1
Withdraw	1.5	1.12 (0.97,1.28)	.1	9.9	1.04 (0.98,1.11)	.1
Stayed On	1.1	0.95 (0.82,1.10)	.5	6.8	0.85 (0.80,0.90)	<.0001

eTable 8. Longer Preoperative Duration of Statin Therapy Logistic Regression Sensitivity Analysis

	Death (N/%)	OR (95% CI)	*P* Value	Cardiac (N/%)	OR (95% CI)	*P* Value	CNS (N/%)	OR (95% CI)	*P* Value
	141811 (2.1)			141488 (0.8)			141616 (0.3)		
Statin Use 6 mos – 1 yr. preadmission	2.1	1.10 (1.00,1.22)	.051	1.0	1.10 (0.94,1.27)	.23	0.4	1.08 (0.85,1.36)	.52
Statin Intensity Group on Admission									
No Statin	2.2	1.0		0.8	1.0		0.3	1.0	
Low	2.2	0.97 (0.82,1.14)	.70	0.9	0.84 (0.65,1.08)	.17	0.3	0.81 (0.54,1.21)	.31
Medium	1.8	0.77 (0.69,0.87)	<.0001	0.8	0.76 (0.64,0.90)	.0013	0.3	0.78 (0.60,1.01)	.062
High	1.9	0.80 (0.69,0.93)	.0042	1.1	0.88 (0.72,1.09)	.24	0.3	0.71 (0.50,1.01)	.056

	Thrombosis (N/%)	OR (95% CI)	*P* Value	Infections (N/%)	OR (95% CI)	*P* Value	Respiratory (N/%)	OR (95% CI)	*P* Value
	141597 (1.2)			141455 (3.7)			140420 (4.4)		
Statin Use 6 mos – 1 yr. preadmission	1.3	1.10 (0.97,1.25)	.14	3.6	1.11 (1.03,1.20)	.006	4.6	1.16 (1.09,1.25)	<.0001
Statin Intensity Group on Admission									
No Statin	1.2	1.0		3.9	1.0		4.5	1.0	
Low	1.3	0.95 (0.77,1,18)	.67	3.4	0.83 (0.73,0.94)	.0046	4.3	0.89 (0.79,1.00)	.055
Medium	1.2	0.92 (0.80,1.05)	.21	3.3	0.79 (0.72,0.86)	<.0001	4.3	0.86 (0.80,0.93)	.0002
High	1.2	0.85 (0.70,1.03)	.098	3.5	0.85 (0.76,0.95)	.0047	4.4	0.87 (0.79,0.97)	.011

	Renal (N/%)	OR (95% CI)	*P* Value	Any Complication (N/%)	OR (95% CI)	*P* Value
	141565 (1.1)			139383 (8.2)		
Statin Use 6 mos – 1 yr. preadmission	1.2	0.97 (0.85,1.11)	.71	8.2	1.12 (1.06,1.17)	<.0001
Statin Intensity Group on Admission						
No Statin	1.0	1.0		1.0		
Low	1.1	0.94 (0.75,1.18)	.60	0.89 (0.81,0.97)	.0073	
Medium	1.2	1.03 (0.89,1.19)	.68	0.85 (0.81,0.91)	<.0001	
High	1.5	1.16 (0.97,1.40)	.10	0.87 (0.80,0.94)	.0003	

Includes statin use 6 months to 1 year prior to admission, 1 year truncated dataset; results adjusted for propensity score, cumulative number of RCRI predictors, consolidated surgical groups and admission prior to surgery.

eTable 9. Socioeconomic Variables Sensitivity Analysis

	Death (N/%)	OR (95% CI)	*P* Value	Cardiac (N/%)	OR (95% CI)	*P* Value	CNS (N/%)	OR (95% CI)	*P* Value
	141811 (2.1)			141488 (0.8)			141616 (0.3)		
Race									
Black	2.0	0.79 (0.71,0.88)	<.0001	0.9	1.13 (0.96,1.32)	.14	0.3	0.92 (0.71,1.20)	.55
Unknown	1.9	0.88 (0.79,0.97)	.014	0.7	0.81 (0.68,0.96)	.016	0.4	1.09 (0.86,1.38)	.48
Other	1.8	0.82 (0.61, 1.13)	.23	0.8	0.90 (0.56,1.47)	.68	0.3	0.95 (0.45, 2.0)	.9
White	2.2	1.0		0.9	1.0		0.3	1.0	
ETOH use	2.1	1.07 (0.93,1.21)	.35	0.8	1.10 (0.89,1.36)	.39	0.3	1.02 (0.73,1.43)	.9
Smoker	2.1	0.84 (0.78,0.92)	<.0001	0.8	0.94 (0.83,1.07)	.34	0.3	1.00 (0.82,1.22)	.97

	Thrombosis (N/%)	OR (95% CI)	*P* Value	Infections (N/%)	OR (95% CI)	*P* Value	Respiratory (N/%)	OR (95% CI)	*P* Value
	141597 (1.2)			141455 (3.7)			140420 (4.4)		
Race									
Black	1.3	1.11 (0.97,1.26)	.12	3.7	0.92 (0.85,0.99)	.033	4.1	0.78 (0.72,0.84)	<.0001
Unknown	1.2	1.00 (0.88,1.14)	.99	3.2	0.85 (0.79,0.93)	.0001	3.9	0.86 (0.80,0.93)	<.0001
Other	0.9	0.77 (0.50,1.18)	.23	3.6	0.91 (0.72,1,14)	.42	4.0	0.86 (0.70,1.07)	.19
White	1.2	1.0		3.8	1.0		4.6	1.0	
ETOH use	1.2	0.98 (0.82,1.17)	.82	3.7	1.21 (1.10,1.32)	<.0001	4.4	1.50 (1.38,1.62)	<.0001
Smoker	1.2	0.74 (0.66,0.82)	<.0001	3.7	1.14 (1.08,1.21)	<.0001	4.4	1.25 (1.18,1.32)	<.0001

eTable 9 (Continued: Socioeconomic Variables Sensitivity Analysis…

	Renal (N/%)	OR (95% CI)	*P* Value	Any Complication (N/%)	OR (95% CI)	*P* Value
	141565 (1.1)			139383 (8.2)		
Race						
Black	1.5	1.50 (1.32,1.70)	<.0001	8.4	0.94 (0.89,1.00)	.034
Unknown	0.9	0.99 (0.86,1.14)	.89	7.2	0.87 (0.82,0.92)	<.0001
Other	1.1	1.10 (0.74,1.64)	.64	7.4	0.87 (0.74,1.02)	.09
White	1.0	1.0		8.5	1.0	
ETOH use	1.1	1.36 (1.15,1.61)	.0003	8,2	1.26 (1.18,1.35)	<.0001
Smoker	1.1	1.01 (0.90,1.12)	.89	8.2	1.11 (1.06,1.16)	<.0001

Includes 1 year truncated dataset, results adjusted for propensity score, statin use and intensity groups on admission, statin use 6 months – 1 year prior to admission, cumulative number of RCRI predictors, consolidated surgical groups and admission prior to surgery

eTable 10. Relative Risks Sensitivity Propensity Model

Outcome	Pairs	Exposed w outcome	Exposed %	Unexposed w outcome	Unexposed %	RR	RR 95%CI	P Value	NNT	NNT 95%CI
Mortality	34999	670	1.9%	858	2.5%	0.78	(0.71,0.86)	0.0001	186	133,312
Cardiac	34757	289	0.8%	414	1.2%	0.70	(0.60,0.81)	0.0001	278	197,475
CNSgroup	34938	164	0.5%	180	0.5%	0.91	(0.74,1.12)	0.416		
Thrombosis	34949	367	1.1%	419	1.2%	0.88	(0.76,1.01)	0.0671		
Infections	34999	1208	3.4%	1461	4.2%	0.83	(0.77,0.89)	0.0001	138	99,228
Respiratory	34213	1340	3.9%	1774	5.1%	0.76	(0.70,0.81)	0.0001	78	63,105
Renal	34858	387	1.1%	481	1.4%	0.80	(0.70,0.92)	0.0015	370	230,951
Any Complication	34999	2951	8.4%	3685	10.5%	0.80	(0.76,0.84)	0.0001	48	40,60

Includes preoperative statin use. RR = relative risk, NNT = number needed to treat, 95% CI = 95% confidence interval,

eMethods. Sensitivity Analyses: Statistical Methods

To evaluate potential drug exposure covariate interactions, a log binomial generalized linear regression model was fit to estimate relative risks using the matched cohort, considering RCRI predictors (cumulative and discrete variables), age greater than or equal to 75 years, and consolidated surgical groupings (vascular, orthopedic, general or a combination of the remaining groups) for all-cause mortality, cardiac and any complication secondary outcomes. 1

Potential associations of statin intensity dosing and patterns of use with outcome were evaluated using logistic regression adjusted for propensity score, cumulative number of RCRI predictors, consolidated surgical groupings (with orthopedic surgery as the reference group), postoperative length of stay groupings (with the shortest stay as the reference group) and an indicator variable for hospital admission prior to the day of surgery in the entire cohort. Generalized estimating equations were used to evaluate clustering within geographical regions or individual hospitals. We found only trivial correlation coefficients for any of these variables and thus conditional logistic regression was used exclusively.

Patients were categorized by patterns of pre-operative statin use, non-use or withdrawal based on analysis of inpatient and outpatient prescription data across our predefined time periods. Patients with active outpatient prescriptions on admission and continued statin exposure in all defined inpatient periods were coded as continuous statin users. Those with an active prescription on admission, but no use during any of the defined inpatient periods, were coded as withdrawn. Patients with no prescription data

either on admission or during any defined inpatient period were coded as non-users, and those with no prescription on admission but a prescriptions in any (or all) of the defined inpatient periods were coded as new statin users. The regression model contained adjustment with an indicator variable for patients admitted prior to the day of surgery (29.2%). Given limitations of the inpatient prescription data in determining the precise duration of an ordered prescription, we coded patients according to whether the inpatient statin prescription appeared to completely cover the period from day of surgery to hospital discharge (complete inpatient coverage), or whether the prescription was present in only a portion of the inpatient time period (partial inpatient coverage).

To evaluate forms of prevalent versus incident user bias (including the potential benefits of longer duration of statin therapy on cardiovascular health), 2 we truncated the original cohort, eliminating the first year of patients. For the remaining subsequent four years, we coded an indicator variable for statin use at any time within the first six months of the year prior to admission. We performed two sensitivity analyses, the first stratifying statin exposed patients from our initial matched cohort by the new indicator variable versus perioperative exposed patients without, considering their respective primary and secondary outcomes. Furthermore, we stratified patients in this group by new prescriptions within 14 day of admission. The second approach utilized logistic regression considering the entire truncated cohort, regressing the new indicator variable along with propensity score, cumulative RCRI variables, statin status on admission (including the potency groupings), aggregated surgical groups and admission prior to surgery. To evaluate potential effects of “healthy user” bias, 2,3 we included three socioeconomic variables available to us in the VASQIP dataset, race, alcohol use and

current smoking in an additional regression model including the aforementioned clinical risk variables.

Given concerns regarding optimal strategies for inclusion of treatment and outcome related variables in propensity models, 4 we performed a sensitivity analysis including availability of statin medication at the time of admission and percent availability within 90 days of admission in our existing propensity model, rematching patients and calculating relative risks for our primary and secondary outcomes as outlined previously.

eResults. Sensitivity Analyses: Results

Clinical Subgroups Drug Exposure Interactions

We explored interaction of surgery type; RCRI number; age; history of diabetes, ischemic heart disease, heart failure, cerebrovascular disease, and renal insufficiency with statin exposure on risk of the primary outcome.(eTable6) No significant interactions were identified. For the secondary outcome of cardiac events, a significant interaction with age was noted with evidence of greater efficacy of statin exposure in patients less than 75 years of age (p=0.009). For the secondary outcome of any complication, significant interactions were noted for ischemic heart disease, diabetes and those undergoing high risk surgery (greater efficacy of statin exposure with presence of each of these characteristics).

Statin Intensity and Patterns of Use

Results of the statin dose intensity and patterns of use sensitivity analysis are presented in eTable7. For the primary outcome, medium and high intensity dosing was associated with improved outcome (O.R. 0.81 (0.75 – 0.89), p <0.0001 and 0.80 (0.71 – 0.91), p = 0.0006 respectively). Classification as a continuous user through the perioperative period was associated with a lower risk of death than classification as non-user, discontinued user, or new user (O.R. 0.68 (0.61 – 0.76), p <0.0001 for indeterminate use pattern and 0.67 (0.60 – 0.75), p < 0.0001 for concordant use pattern). A significant association of high intensity dosing with renal injury (p < 0.03) was noted in the statin on admit group and a borderline association (p < 0.054) was noted in the any statin use within 90 days preoperatively. The risk of primary or secondary outcomes was greater

with increasing RCRI factors, vascular or general surgery (relative to orthopedic surgery), longer postoperative length of stay, and admission to hospital prior to day of surgery in all of the models, consistent with the expected directionality of these important clinical covariates (data not shown).

Antecedent and New User Effects

To evaluate the potential impact of longer periods of statin therapy (6 months to 1 year prior to admission) on outcome, as well as the validity of our assumptions regarding new users (eg. new use within 14 days of admission indicator), our one year truncated cohort consisted of 142,054 patients. Of these 45.8% were noted to have prescriptions within six to 12 months of admission. Of the 1360 patients in this cohort identified as a potential new user within 14 days of admission (using our 90 day window), 78.3% were found to have a prior prescription in the six to 12 month prior window, suggesting a lapse in therapy.

Considering subsets of our existing propensity matched cohort relative to the prior six to 12 month use variable, we noted no significant differences in outcome between chronic and less chronic exposed users for any of our primary or secondary outcomes (n = 38,581 for the mortality subset)(data not shown). Consideration of the small strata of new users within 14 days (0.9%) in a similar manner also revealed no significant differences. Utilizing the regression approach to the entire truncated cohort described above (n = 141,811) yielded borderline significance for a small increase in risk of the primary outcome (O.R. 1.10, 1.00 – 1.22, p = 0.051), no significant influence on the risk of cardiac, CNS, thrombotic, or renal outcomes, but significant small increases for

infections (O.R. 1.11, 1.03 – 1.20, p = 0.0063), respiratory (O.R. 1.16, 1.09 – 1.25, p <0.001) and aggregate complications (1.12, 1.06 – 1.17, p <0.001).(eTable8).

Healthy User Bias

Considering the socioeconomic variables used to model potential healthy user effects described above, as presented in eTable9, for the primary outcome, black race and smoking were associated with significantly *lower* risks (O.R. 0.79, 0.71 – 0.88, p < 0.0001; O.R. 0.84, 0.78 – 0.92, p < 0.0001 respectively), although ETOH use was not significant. The significance and directionality of other clinical risk variables were similar to our subgroup interaction analyses, conforming to expected clinical results. The results for the secondary outcomes however, are in general, more consistent with a healthy user effect.

Propensity Model

The results of the revised propensity model incorporating statin use at admission and percent of use within 90 days of admission are presented in eTable10. We noted a substantially lower matching rate (34,999 pairs) along with higher average standardized differences including 2 variables marginally exceeding our 10% threshold (data not shown). Despite this, nearly identical relative risks were noted for the primary and secondary outcomes.

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