**Supplementary Digital Content**

**SUPPLEMENTAL TABLE I.** ICD-9 codes used for comorbidities and complications

|  |  |
| --- | --- |
| **Comorbidity** | **ICD-9 Code** |
| Myocardial Infarction | 410.xx, 412.xx |
| Deep Vein Thrombosis | 415.11, 415.19 |
| Pulmonary Embolism | 451.1x, 451.2x, 451.8x, 451.9x, 453.2x, 453.4x, 453.8x, 453.9x |
| Ischemic Stroke or Transient Ischemic Attack | 336.1x, 362.31, 362.32, 362.34, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.0x-435.3x, 435.8x, 435.9x |
| Seizure | 780.39 |
| Atrial Fibrillation | 427.31 |
| Renal Disease | 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.xx-583.7x, 584.xx, 585.xx, 586.xx, 588.0x, V42.0, V45.1, V56.x |
|   |   |
| Congestive Heart Failure | 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4x, 425.5x, 425.7x, 425.8x, 425.9x, 428.xx |
| Peripheral Vascular Disease | 093.0x, 437.3x, 440.xx, 441.xx, 443.1x-443.9x, 447.1x, 557.1x, 557.9x, V43.4 |
| Cerebrovascular Disease | 362.34, 430.xx-438.xx |
| Dementia | 290.xx, 294.1x, 331.2x |
| Chronic Obstructive Pulmonary Disease | 416.8x, 416.9x, 490.xx-505.xx, 506.4x, 508.1x, 508.8x |
| Rheumatic Disease | 446.5x, 710.0x-710.4x, 714.0x-714.2x, 714.8x, 725.xx |
| Peptic Ulcer Disease | 531.xx-534.xx |
| Mild Liver Disease | 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6x, 070.9x, 570.xx, 571.xx, 573.3x, 573.4x, 573.8x, 573.9x, V42.7 |
| Diabetes without complications | 250.0x-250.3x, 250.8x, 250.9x |
| Diabetes with chronic complications | 250.4x-250-7x |
| Hemiplegia or Paraplegia | 334.1x, 342.xx-344.xx |
| Renal Disease |   |
| Malignancy | 140.xx-165.xx, 170.xx-195.xx, 200.xx-208.xx, 238.6x |
| Moderate or Severe Liver Disease | 456.0x-456.2x, 572.2x-572.8x |
| Metastatic Cancer | 196.xx-199.xx |
| AIDS | 042.xx-044.xx |
| History of Substance Use/Abuse | 265.2x, 291.1x-291.5x, 291.8x, 291.9x, 292.xx, 303.xx, 304.xx, 305.xx, 357.5x, 425.5x, 535.3x, 517.0x-571.3x, 649.0x, 980.xx, V11.3, V15.82, V65.42 |
| Chronic Pain Conditions | 140.xx, 175.xx, 179.xx-203.0x, 238.6x, 338.0x, 338.2x, 338.4x, 339.xx, 346.xx, 648.7x, 714.xx, 720.xx-724.xx, 729.1x, 738.4x, 739.3x, 739.4x, 756.11, 756.12, 784.0x, 805.xx, 846.xx, 847.xx |
| Psychiatric Comorbidities | 290.xx, 293.8x, 294.1x, 295.xx, 296.04x, 296.14, 296.2x, 296.3x,296.44, 296.5x, 297.xx, 298.xx, 300.0x, 300.2x-300.4x, 301.xx, 308.0x, 309.xx, 311.xx, 331.2x |
| Opioid Use Disorder | 304.0x, 304.7x, 305.5x |
| Obstructive Sleep Apnea | 278.03, 327.20, 327.21, 327.23, 327.27, 327.29, 780.51, 780.53, 780.57 |
| **Complication** | **ICD-9 Code** |
| Myocardial Infarction | 410.xx |
| Pulmonary Embolism | 415.11, 415.19 |
| Deep Vein Thrombosis | 451.1x, 451.2x, 451.8x, 451.9x, 453.2x, 453.4x, 453.8x, 453.9x |
| Ischemic Stroke or Transient Ischemic Attack | 336.1x, 362.31, 362.32, 362.34, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.0x-435.3x, 435.8x, 435.9x |
| Seizure | 780.39 |
| Acute Renal Failure | 584.xx |

**SUPPLEMENTAL TABLE II.** Dosing characteristics and outcomes by tranexamic acid use in elective total hip and knee arthroplasty patients without a history of VTE, MI, Seizures, or Ischemic Stroke/Transient Ischemic Attack

|  |  |
| --- | --- |
|  | **NON-HIGH-RISK DEFINITION I: NO HISTORY OF VTE, MI, SEIZURES, ISCHEMIC STROKE/TRANSIENT ISCHEMIC ATTACK** |
|  | **Tranexamic Acid Use** |  |  |
|   | **Yes (n=391,970)** | **No (n=345,151)** | **p-value** | **Standardized****Difference** |
| **Dose** |   |   |   |   |
| 1,000 mg | 115,243 (29.4%) | **-** | **-** | **-** |
| 2,000 mg | 201,586 (51.4%) | **-** | **-** | **-** |
| ≥ 3,000 mg | 52,838 (13.5%) | **-** | **-** | **-** |
| Not Specified | 22,303 (5.7%) | **-** | **-** | **-** |
| **OUTCOMES** |   |   |   |   |
| **Blood Transfusion** | 15,850 (4.0%) | 43,326 (12.6%) | <0.001 | 0.312 |
|  |  |  |  |   |
| ***Complications*** |  |  |  |   |
| **New Onset Deep Venous Thrombosis** | 641 (0.2%) | 978 (0.3%) | <0.001 | 0.025 |
| **New Onset Pulmonary Embolism** | 627 (0.2%) | 973 (0.3%) | <0.001 | 0.026 |
| **New Onset MI** | 263 (0.1%) | 479 (0.1%) | <0.001 | 0.022 |
| **New Onset Seizures** | 47 (0.0%) | 64 (0.0%) | 0.0222 | 0.005 |
| **New Onset Ischemic Stroke/Transient Ischemic Attack** | 209 (0.1%) | 312 (0.1%) | <0.001 | 0.014 |
| **New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack (‘Composite Complications’)** | 1,651 (0.4%) | 2,586 (0.7%) | <0.001 | 0.043 |
| **New Onset Acute Renal Failure** | 4,806 (1.2%) | 7,330 (2.1%) | <0.001 | 0.070 |
| **90-Day Readmission due to Any of the Above (New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack or Acute Renal Failure)** | 472 (0.1%) | 532 (0.2%) | <0.001 | 0.009 |
| **In-Hospital Mortality** | 64 (0.0%) | 242 (0.1%) | <0.001 | 0.026 |
|   |  |  |  |   |
| ***Resource Utilization*** |  |  |  |   |
| **Length of Stay\*** | 2 (2-3) | 3 (2-3) | <0.001 | 0.339 |
| **Cost of Hospitalization\*** | $15,473 ($12,847-$19,016) | $16,241 ($13,340-$20,173) | <0.001 | 0.100 |

\*Continuous variable, median and interquartile range instead of N and %

VTE: represents deep venous thrombosis and pulmonary embolism

**SUPPLEMENTAL TABLE III.** Dosing characteristics and outcomes by tranexamic acid use in elective total hip and knee arthroplasty patients without a history of renal disease

|  |  |
| --- | --- |
|  | **NON-** **HIGH-RISK DEFINITION II: NO HISTORY OF RENAL DISEASE** |
|  | **Tranexamic Acid Use** |  |  |
|   | **Yes (n=382,550)** | **No (n=337,853)** | **p-value** | **Standardized Difference** |
| **Dose** |   |   |   |   |
| 1,000 mg | 112,566 (29.4%) | **-** | **-** | **-** |
| 2,000 mg | 196,467 (51.4%) | **-** | **-** | **-** |
| ≥ 3,000 mg | 51,622 (13.5%) | **-** | **-** | **-** |
| Not Specified or N/A | 21,895 (5.7%) | **-** | **-** | **-** |
| **OUTCOMES** |   |   |   |   |
| **Blood Transfusion** | 14,526 (3.8%) | 40,460 (12.0%) | <0.001 | 0.307 |
|  |  |  |  |   |
| ***Complications*** |  |  |  |   |
| **New Onset Deep Venous Thrombosis** | 597 (0.2%) | 913 (0.3%) | <0.001 | 0.025 |
| **New Onset Pulmonary Embolism** | 597 (0.2%) | 931 (0.3%) | <0.001 | 0.026 |
| **New Onset MI** | 251 (0.1%) | 454 (0.1%) | <0.001 | 0.022 |
| **New Onset Seizures** | 38 (0.0%) | 59 (0.0%) | 0.006 | 0.006 |
| **New Onset Ischemic Stroke/Transient Ischemic Attack** | 184 (0.0%) | 297 (0.1%) | <0.001 | 0.015 |
| **New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack (‘Composite Complications’)** | 1,542 (0.4%) | 2,456 (0.7%) | <0.001 | 0.043 |
| **New Onset Acute Renal Failure** | 3,065 (0.8%) | 4,828 (1.4%) | <0.001 | 0.060 |
| **90-Day Readmission due to Any of the Above (New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack or Acute Renal Failure)** | 430 (0.1%) | 503 (0.1%) | <0.001 | 0.010 |
| **In-Hospital Mortality** | 57 (0.0%) | 193 (0.1%) | <0.001 | 0.022 |
|  |  |  |  |   |
| ***Resource Utilization*** |  |  |  |   |
| **Length of Stay\*** | 2 (2-3) | 3 (2-3) | <0.001 | 0.346 |
| **Cost of Hospitalization\*** | $15,443 ($12,828-$18,957) | $16,187 ($13,305-$20,077) | <0.001 | 0.098 |

\*Continuous variable, median and interquartile range instead of N and %

VTE: represents deep venous thrombosis and pulmonary embolism

**SUPPLEMENTAL TABLE IV.** Dosing characteristics and outcomes by tranexamic acid use in elective total hip and knee arthroplasty patients without a history of atrial fibrillation

|  |  |
| --- | --- |
|  | **NON-** **HIGH-RISK DEFINITION III: NO HISTORY OF ATRIAL FIBRILLATION** |
|  | **Tranexamic Acid Use** |  |  |
|   | **Yes (n=382,595)** | **No (n=336,464)** | **p-value** | **Standardized Difference** |
| **Dose** |   |   |   |   |
| 1,000 mg | 112,563 (29.4%) | **-** | **-** | **-** |
| 2,000 mg | 196,738 (51.4%) | **-** | **-** | **-** |
| ≥ 3,000 mg | 51,511 (13.5%) | **-** | **-** | **-** |
| Not Specified or N/A | 21,783 (5.7%) | **-** | **-** | **-** |
| **OUTCOMES** |   |   |   |   |
| **Blood Transfusion** | 15,246 (4.0%) | 41,846 (12.4%) | <0.001 | 0.312 |
|  |  |  |  |   |
| ***Complications*** |  |  |  |   |
| **New Onset Deep Venous Thrombosis** | 608 (0.2%) | 945 (0.3%) | <0.001 | 0.026 |
| **New Onset Pulmonary Embolism** | 585 (0.2%) | 934 (0.3%) | <0.001 | 0.027 |
| **New Onset MI** | 283 (0.1%) | 520 (0.2%) | <0.001 | 0.024 |
| **New Onset Seizures** | 47 (0.0%) | 61 (0.0%) | <0.001 | 0.005 |
| **New Onset Ischemic Stroke/Transient Ischemic Attack (‘Composite Complications’)** | 193 (0.1%) | 294 (0.1%) | <0.001 | 0.014 |
| **New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack** | 1,593 (0.4%) | 2,535 (0.8%) | <0.001 | 0.044 |
| **New Onset Acute Renal Failure** | 4,535 (1.2%) | 6,837 (2.0%) | <0.001 | 0.067 |
| **90-Day Readmission due to Any of the Above (New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack or Acute Renal Failure)** | 467 (0.1%) | 530 (0.2%) | <0.001 | 0.001 |
| **In-Hospital Mortality** | 61 (0.0%) | 216 (0.1%) | <0.001 | 0.024 |
|  |  |  |  |   |
| ***Resource Utilization*** |  |  |  |   |
| **Length of Stay\*** | 2 (2-3) | 3 (2-3) | <0.001 | 0.342 |
| **Cost of Hospitalization\*** | $15,458 ($12,834-$18,993) | $16,222 ($13,322-$20,137) | <0.001 | 0.098 |

\*Continuous variable, median and interquartile range instead of N and %

STD: standardized difference / VTE: represents deep venous thrombosis and pulmonary embolism

**SUPPLEMENTAL TABLE V.** Results from multivariable models in non-high-risk groups in elective total hip and knee arthroplasty patients; effect estimates (odds ratios for binary outcome variables, % change for continuous outcome variables) for tranexamic acid use (reference = no use) without history of VTE, MI, Seizures, or Ischemic Stroke/Transient Ischemic Attack (left side); without history of renal disease (center); without history of atrial fibrillation (right side).

|  |  |  |  |
| --- | --- | --- | --- |
|  | **NON-HIGH-RISK DEFINITION I: NO HISTORY OF VTE, MI, SEIZURES, ISCHEMIC STROKE/TRANSIENT ISCHEMIC ATTACK** | **NON-HIGH-RISK DEFINITION II: NO HISTORY OF RENAL DISEASE** | **NON-HIGH-RISK DEFINITION III: NO HISTORY OF ATRIAL FIBRILLATION** |
|  | ***Tranexamic acid use [reference: no use]*** | ***Tranexamic acid use [reference: no use]*** | ***Tranexamic acid use [reference: no use]*** |
|  | **OR / % Change (99.9% CI)** | **p-value** | **OR / % Change (99.9% CI)** | **p-value** | **OR / % Change (99.9% CI)** | **p-value** |
| **OUTCOMES** |  |  |  |   |  |  |
| **Blood Transfusion** | 0.310 (0.266; 0.361) | <0.0001 | 0.311 (0.267; 0.362) | <0.001 | 0.310 (0.267; 0.361) | <0.001 |
|  |   |   |  |   |  |   |
| ***Complications*** |   |   |  |   |  |   |
| **New Onset Deep Venous Thrombosis** | 0.89 (0.43; 1.87) | >0.999 | 0.89 (0.43; 1.87) | >0.999 | 0.89 (0.43; 1.86) | >0.999 |
| **New Onset Pulmonary Embolism** | 0.73 (0.315; 1.71) | >0.999 | 0.74 (0.318; 1.72) | >0.999 | 0.73 (0.313; 1.68) | >0.999 |
| **New Onset MI** | 0.91 (0.374; 2.22) | >0.999 | 0.92 (0.375; 2.24) | >0.999 | 0.89 (0.368; 2.17) | >0.999 |
| **New Onset Seizures** | 0.90 (0.094; 8.7) | >0.999 | 0.94 (0.098; 9.2) | >0.999 | 0.93 (0.095; 9.1) | >0.999 |
| **New Onset Ischemic Stroke/Transient Ischemic Attack** | 1.07 (0.41; 2.81) | >0.999 | 1.06 (0.40; 2.81) | >0.999 | 1.15 (0.43; 3.06) | >0.999 |
| **New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack (‘Composite Complications’)** | 0.89 (0.57; 1.40) | >0.999 | 0.87 (0.55; 1.37) | >0.999 | 0.88 (0.56; 1.37) | >0.999 |
| **New Onset Acute Renal Failure** | 0.68 (0.52; 0.89) | <0.001 | 0.69 (0.53; 0.91) | <0.001 | 0.72 (0.55; 0.94) | <0.001 |
| **90-Day Readmission due to Any of the Above (New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack or Acute Renal Failure)** | 1.01 (0.51; 1.99) | >0.999 | 1.00 (0.51; 1.97) | >0.999 | 1.08 (0.55; 2.13) | >0.999 |
| **In-Hospital Mortality** | 0.61 (0.127; 2.96) | >0.999 | 0.66 (0.140; 3.11) | >0.999 | 0.65 (0.139; 3.05) | >0.999 |
|  |   |   |   |   |  |   |
| ***Resource Utilization*** |   |   |   |   |  |   |
| **Length of Stay\*** | -1.2% (-2.5; 0.2%) | 0.274 | -1.1% (-2.5; 0.2%) | 0.310 | -1.3% (-2.6; 0.1%) | 0.108 |
| **Cost of Hospitalization\*** | -0.7% (-2.4; 1.1%) | >0.999 | -0.6% (-2.3; 1.1%) | >0.999 | -0.8% (-2.5; 1.0%) | >0.999 |

Models adjusted for age, sex, race, insurance type, hospital location, bed size, teaching status, annual volume of joint arthroplasty procedures, year and type of procedure, anesthesia type, use of patient controlled analgesia, NSAIDs, cyclooxygenase-2 inhibitors, ketamine, pregabalin/gabapentin, acetaminophen, peripheral nerve blocks, history of VTE, MI, seizures, ischemic stroke/transient ischemic attack, renal disease, atrial fibrillation, Charlson comorbidities (not overlapping with aforementioned comorbidities), use of anticoagulants, history of substance use/abuse, chronic pain conditions, psychiatric comorbidities, opioid use disorder and obstructive sleep apnea.

P-values are Bonferroni adjusted and reflect testing of 72 hypotheses.

**SUPPLEMENTAL TABLE VI.** Results from sensitivity analyses (using a cohort only including hospitals with ≥75% hospital-specific tranexamic acid use) for elective total hip and knee arthroplasty patients; effect estimates (odds ratios for binary outcome variables, % change for continuous outcome variables) from multivariable models for tranexamic acid use (reference = no use) by history of VTE, MI, Seizures, or Ischemic Stroke/Transient Ischemic Attack.

|  |  |
| --- | --- |
|  | **HIGH-RISK DEFINITION I: HISTORY OF VTE, MI, SEIZURES, ISCHEMIC STROKE/TRANSIENT ISCHEMIC ATTACK** |
|  | **HIGH-RISK** | **NON-HIGH-RISK** |
|  | ***Tranexamic acid use [reference: no use]*** | ***Tranexamic acid use [reference: no use]*** |
|  | **OR / % Change (99.9% CI)** | **p-value** | **OR / % Change (99.9% CI)** | **p-value** |
| **OUTCOMES** |  |  |  |  |
| **Blood Transfusion** | 0.361 (0.221; 0.59) | <0.001 | 0.42 (0.296; 0.59) | <0.001 |
|  |   |   |  |   |
| ***Complications*** |   |   |  |   |
| **New Onset Deep Venous Thrombosis** | 1.25 (0.168; 9.3) | >0.999 | 1.09 (0.335; 3.54) | >0.999 |
| **New Onset Pulmonary Embolism** | 0.393 (0.042; 3.66) | >0.999 | 1.10 (0.216; 5.63) | >0.999 |
| **New Onset MI** | 0.61 (0.093; 3.99) | >0.999 | 0.96 (0.189; 4.9) | >0.999 |
| **New Onset Seizures** | 0.58 (0.000; 1670.4) | >0.999 | 0.50 (0.006; 39.6) | >0.999 |
| **New Onset Ischemic Stroke/Transient Ischemic Attack** | 0.77 (0.047; 12.7) | >0.999 | 0.74 (0.115; 4.8) | >0.999 |
| **New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack (‘Composite Complications’)** | 0.78 (0.41; 1.46) | >0.999 | 0.76 (0.49; 1.18) | >0.999 |
| **New Onset Acute Renal Failure** | 0.96 (0.47; 1.96) | >0.999 | 0.78 (0.48; 1.27) | >0.999 |
| **90-Day Readmission due to Any of the Above (New Onset VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack or Acute Renal Failure)** | 1.06 (0.116; 9.7) | >0.999 | 0.84 (0.281; 2.52) | >0.999 |
| **In-Hospital Mortality** | 0.254 (0.007; 8.4) | >0.999 | 0.399 (0.037; 4.3) | >0.999 |
|  |   |   |  |   |
| ***Resource Utilization*** |   |   |  |   |
| **Length of Stay\*** | -4.6% (-9.5; 0.6%) | 0.202 | -6.4% (-8.9; -3.7%) | <0.001 |
| **Cost of Hospitalization\*** | -0.9% (-5.0; 3.4%) | >0.999 | -3.3% (1.1; -3.7%) | >0.999 |

Models adjusted for age, sex, race, insurance type, hospital location, bed size, teaching status, annual volume of joint arthroplasty procedures, year and type of procedure, anesthesia type, use of patient controlled analgesia, NSAIDs, cyclooxygenase-2 inhibitors, ketamine, pregabalin/gabapentin, acetaminophen, peripheral nerve blocks, history of VTE, MI, seizures, ischemic stroke/transient ischemic attack, renal disease, atrial fibrillation, Charlson comorbidities (not overlapping with aforementioned comorbidities), use of anticoagulants, history of substance use/abuse, chronic pain conditions, psychiatric comorbidities, opioid use disorder and obstructive sleep apnea.

P-values are Bonferroni adjusted and reflect testing of 72 hypotheses.