

Supplementary Online Content

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eTable 1. All-cause Mortality and Short-term Safety Outcomes After Total Knee Replacement Among Intermittent Opioid Users vs Opioid-Naive Patients

eTable 2. Patient Characteristics Prior to Total Knee Replacement Excluding Patients With Malignant Tumors

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. All-cause Mortality and Short-term Safety Outcomes After Total Knee Replacement Among Intermittent Opioid Users vs Opioid-Naive Patients

| | Unadjusted model HR (95%CI) | Model 1 HR (95%CI) | Model 2 HR (95%CI) |
|---------------------------------|--|-------------------------------|-------------------------------|
| All-cause mortality | | | |
| <i>In hospital</i> | 1.65 (1.26-2.15) | 1.76 (1.35-2.30) | 1.20 (0.90-1.59) |
| 30 days | 1.39 (1.16-1.67) | 1.49 (1.24-1.80) | 1.10 (0.90-1.34) |
| 60 days | 1.41 (1.19-1.66) | 1.52 (1.28-1.80) | 1.10 (0.91-1.31) |
| 90 days | 1.32 (1.13-1.54) | 1.43 (1.22-1.67) | 1.02 (0.86-1.21) |
| Hospital Readmission | | | |
| 30 days | 1.18 (1.13-1.23) | 1.21 (1.15-1.26) | 0.99 (0.94-1.04) |
| 60 days | 1.19 (1.15-1.24) | 1.22 (1.18-1.27) | 1.00 (0.96-1.04) |
| 90 days | 1.20 (1.16-1.24) | 1.23 (1.19-1.27) | 1.02 (0.99-1.06) |
| Revision surgery | | | |
| 30 days | 1.60 (1.31-1.96) | 1.63 (1.33-2.00) | 1.29 (1.04-1.61) |
| 60 days | 1.53 (1.30-1.81) | 1.56 (1.32-1.84) | 1.23 (1.03-1.46) |
| 90 days | 1.50 (1.29-1.75) | 1.53 (1.31-1.78) | 1.23 (1.05-1.45) |
| Opioid overdose | | | |
| 30 days | 3.88 (1.47-10.20) | 3.89 (1.47-10.26) | 3.07 (1.12-8.40) |
| 60 days | 4.23 (1.62-11.05) | 4.30 (1.64-11.26) | 3.30 (1.22-8.92) |
| 90 days | 4.58 (1.76-11.90) | 4.70 (1.80-12.22) | 3.48 (1.31-9.26) |
| Non-vertebral fracture | | | |
| 30 days | 1.82 (0.99-3.36) | 1.79 (0.96-3.31) | 1.46 (0.76-2.81) |
| 60 days | 1.43 (0.99-2.07) | 1.43 (0.98-2.07) | 1.20 (0.81-1.78) |
| 90 days | 1.34 (1.02-1.75) | 1.37 (1.04-1.80) | 1.16 (0.86-1.55) |
| Vertebral fracture | | | |
| 30 days | 2.07 (1.44-2.98) | 2.15 (1.48-3.14) | 1.54 (1.04-2.28) |
| 60 days | 1.74 (1.38-2.20) | 1.78 (1.40-2.27) | 1.33 (1.03-1.71) |
| 90 days | 1.80 (1.49-2.16) | 1.83 (1.51-2.21) | 1.36 (1.11-1.66) |
| Myocardial infarction or stroke | | | |
| 30 days | 1.14 (0.85-1.51) | 1.23 (0.92-1.64) | 0.98 (0.72-1.33) |
| 60 days | 1.21 (0.94-1.57) | 1.32 (1.02-1.71) | 1.09 (0.83-1.44) |
| 90 days | 1.25 (0.99-1.59) | 1.37 (1.08-1.74) | 1.10 (0.85-1.42) |
| Respiratory distress | | | |
| 30 days | 1.86 (1.01-3.42) | 1.84 (1.00-3.41) | 1.26 (0.66-2.42) |
| 60 days | 1.70 (1.02-2.83) | 1.70 (1.02-2.85) | 1.12 (0.65-1.94) |
| 90 days | 1.19 (0.76-1.85) | 1.18 (0.75-1.85) | 0.79 (0.49-1.28) |

| | | | |
|--------------------------|------------------|------------------|------------------|
| | | | |
| Pneumonia | | | |
| <i>30 days</i> | 1.13 (0.86-1.50) | 1.18 (0.89-1.56) | 0.81 (0.60-1.10) |
| <i>60 days</i> | 1.08 (0.85-1.37) | 1.12 (0.88-1.43) | 0.77 (0.59-1.00) |
| <i>90 days</i> | 1.22 (0.98-1.53) | 1.28 (1.02-1.60) | 0.86 (0.68-1.09) |
| | | | |
| Bowel obstruction | | | |
| <i>30 days</i> | 1.27 (0.89-1.79) | 1.32 (0.93-1.87) | 1.10 (0.76-1.61) |
| <i>60 days</i> | 1.28 (0.95-1.72) | 1.32 (0.98-1.78) | 1.10 (0.80-1.51) |
| <i>90 days</i> | 1.32 (1.02-1.72) | 1.37 (1.05-1.78) | 1.14 (0.86-1.51) |

Model 1 is adjusted for age, sex, race/ethnicity and region of residence. Model 2 is adjusted for comorbidity index, frailty, and number of unique prescription drugs in addition to the variables in the Model 1.

eTable 2. Patient Characteristics Prior to Total Knee Replacement Excluding Patients With Malignant Tumors

| | Continuous users (n=19,241) | Intermittent users (n=129,685) | Opioid-naïve (n=107,627) |
|---|--|---|-------------------------------------|
| <i>Presented as percentage or mean ± SD</i> | | | |
| <i>Demographics</i> | | | |
| Age, years | 72.5 ± 5.6 | 73.5 ± 5.7 | 74.0 ± 5.8 |
| Female | 14,984 (77.9) | 94,130 (72.6) | 71,688 (66.6) |
| <i>Race/ethnicity</i> | | | |
| White | 16,875 (87.7) | 114,625 (88.4) | 98,262 (91.3) |
| Black | 1,648 (8.6) | 7,880 (6.1) | 3,948 (3.7) |
| Hispanic | 277 (1.4) | 3,007 (2.3) | 1,588 (1.5) |
| Other | 271 (1.4) | 2,390 (1.8) | 2,052 (1.9) |
| <i>Region</i> | | | |
| Northeast | 1,978 (10.3) | 17,488 (13.5) | 19,495 (18.1) |
| Midwest | 4,986 (25.9) | 35,562 (27.4) | 34,343 (31.9) |
| South | 8,732 (45.4) | 52,282 (40.3) | 36,021 (33.5) |
| West | 3,539 (18.4) | 24,107 (18.6) | 17,544 (16.3) |
| <i>Comorbidities</i> | | | |
| Hypertension | 17,274 (89.8) | 111,792 (86.2) | 87,327 (81.1) |
| Diabetes | 7,388 (38.4) | 44,010 (33.9) | 30,775 (28.6) |
| Obesity | 4,441 (23.1) | 25,136 (19.4) | 15,088 (14.0) |
| Back pain | 13,680 (71.1) | 68,409 (52.8) | 37,990 (35.3) |
| Neuropathic pain | 8,591 (44.6) | 41,798 (32.2) | 19,859 (18.5) |
| Coronary heart disease | 2,155 (11.2) | 11,376 (8.8) | 6,723 (6.2) |
| Chronic kidney disease | 2,966 (15.4) | 15,071 (11.6) | 8,395 (7.8) |
| Heart failure | 2,922 (15.2) | 12,865 (9.9) | 6,629 (6.2) |
| Hip fracture | 89 (0.5) | 533 (0.4) | 201 (0.2) |
| Migraine | 3,009 (15.6) | 14,416 (11.1) | 6,825 (6.3) |
| Sleep disorder | 5,227 (27.2) | 26,101 (20.1) | 14,390 (13.4) |
| Depression | 6,020 (31.3) | 23,301 (18.0) | 10,912 (10.1) |
| Anxiety disorder | 4,562 (23.7) | 17,134 (13.2) | 8,217 (7.6) |
| Bipolar disorder | 509 (2.6) | 1,714 (1.3) | 749 (0.7) |
| Drug abuse | 249 (1.3) | 279 (0.2) | 50 (0.0) |
| Alcohol abuse | 304 (1.6) | 1,228 (0.9) | 614 (0.6) |
| Tobacco use | 4,020 (20.9) | 17,997 (13.9) | 9,611 (8.9) |
| Rheumatoid arthritis | 2,032 (10.6) | 7,992 (6.2) | 3,558 (3.3) |
| <i>Frailty</i> | | | |
| Robust | 2,951 (15.3) | 42,041 (32.4) | 53,625 (49.8) |
| Prefrail | 12,603 (65.5) | 77,858 (60.0) | 51,616 (48.0) |

| | | | |
|-----------------------------------|---------------|---------------|---------------|
| Mild frailty | 3,367 (17.5) | 9,040 (7.0) | 2,272 (2.1) |
| Moderate-to-severe frailty | 320 (1.7) | 746 (0.6) | 114 (0.1) |
| Comorbidity index | 1.6 ± 2.4 | 1.1 ± 2.1 | 0.6 ± 1.7 |
| <i>Medication use</i> | | | |
| NSAIDs | 9,034 (47.0) | 59,123 (45.6) | 32,341 (30.0) |
| Coxibs | 2,340 (12.2) | 15,054 (11.6) | 8,042 (7.5) |
| Oral corticosteroids | 8,816 (45.8) | 51,399 (39.6) | 29,935 (27.8) |
| Antidepressants | 10,443 (54.3) | 43,783 (33.8) | 21,700 (20.2) |
| Benzodiazepines | 4,230 (22.0) | 15,080 (11.6) | 6,600 (6.1) |
| Bisphosphonates | 1,529 (7.9) | 9,965 (7.7) | 7,222 (6.7) |
| Anticonvulsants | 7,639 (39.7) | 25,843 (19.9) | 9,460 (8.8) |
| <i>Health care utilization</i> | | | |
| No. of unique prescription drugs | 15.4 ± 6.7 | 12.1 ± 5.6 | 7.7 ± 4.5 |
| No. of emergency department visit | 0.8 ± 1.8 | 0.5 ± 1.1 | 0.2 ± 0.6 |
| No. of visits to any physicians | 15.7 ± 9.4 | 13.3 ± 7.6 | 10.1 ± 6.2 |
| No. of acute hospitalization | 0.4 ± 0.2 | 0.3 ± 0.1 | 0.1 ± 0.1 |

eTable 3. All-cause Mortality and Short-term Safety Outcomes After Total Knee Replacement Among Continuous Opioid Users vs Opioid-Naive Patients Excluding Patients With Malignant Tumors

| | Unadjusted HR (95% CI) | Model 1 HR (95% CI) | Model 2 HR (95%CI) |
|---------------------------------|-----------------------------------|--------------------------------|-------------------------------|
| All-cause mortality | | | |
| <i>In hospital</i> | 1.61 (0.97, 2.68) | 1.95 (1.17, 3.25) | 0.98 (0.56, 1.69) |
| 30 days | 1.33 (0.91, 1.95) | 1.65 (1.12, 2.42) | 0.95 (0.63, 1.43) |
| 60 days | 1.56 (1.12, 2.16) | 1.95 (1.40, 2.71) | 1.08 (0.76, 1.54) |
| 90 days | 1.45 (1.06, 1.98) | 1.81 (1.32, 2.48) | 1.00 (0.71, 1.40) |
| Hospital Readmission | | | |
| 30 days | 1.48 (1.36, 1.62) | 1.57 (1.44, 1.72) | 1.05 (0.96, 1.16) |
| 60 days | 1.58 (1.47, 1.69) | 1.67 (1.55, 1.79) | 1.12 (1.03, 1.21) |
| 90 days | 1.62 (1.52, 1.73) | 1.71 (1.61, 1.83) | 1.17 (1.10, 1.26) |
| Revision surgery | | | |
| 30 days | 2.72 (1.96, 3.77) | 2.74 (1.96, 3.83) | 1.66 (1.15, 2.40) |
| 60 days | 2.24 (1.69, 2.95) | 2.32 (1.75, 3.07) | 1.38 (1.01, 1.89) |
| 90 days | 2.31 (1.79, 2.98) | 2.38 (1.84, 3.09) | 1.49 (1.12, 1.98) |
| Opioid overdose | | | |
| 30 days | 7.36 (2.25, 24.13) | 7.04 (2.12, 23.39) | 3.65 (0.98, 13.66) |
| 60 days | 11.16 (3.74, 33.31) | 10.99 (3.64, 33.23) | 5.66 (1.68, 19.05) |
| 90 days | 18.83 (6.84, 51.82) | 19.41 (6.98, 54.01) | 9.60 (3.16, 29.15) |
| Non-vertebral fracture | | | |
| 30 days | 3.21 (1.20, 8.55) | 3.36 (1.25, 9.03) | 2.25 (0.75, 6.70) |
| 60 days | 1.67 (0.84, 3.35) | 1.67 (0.83, 3.36) | 1.13 (0.53, 2.42) |
| 90 days | 2.03 (1.26, 3.28) | 2.15 (1.33, 3.50) | 1.49 (0.88, 2.53) |
| Vertebral fracture | | | |
| 30 days | 4.25 (2.51, 7.20) | 4.54 (2.65, 7.78) | 2.32 (1.28, 4.21) |
| 60 days | 4.29 (3.05, 6.02) | 4.58 (3.24, 6.48) | 2.44 (1.66, 3.60) |
| 90 days | 4.53 (3.45, 5.94) | 4.77 (3.62, 6.29) | 2.47 (1.82, 3.36) |
| Myocardial infarction or stroke | | | |
| 30 days | 0.84 (0.42, 1.69) | 1.04 (0.52, 2.10) | 0.72 (0.34, 1.50) |
| 60 days | 0.94 (0.51, 1.72) | 1.17 (0.63, 2.15) | 0.85 (0.45, 1.62) |

| | | | |
|----------------------|--------------------------|--------------------------|--------------------------|
| 90 days | 1.14 (0.68, 1.91) | 1.43 (0.85, 2.40) | 0.93 (0.54, 1.62) |
| | | | |
| Respiratory distress | | | |
| 30 days | 2.06 (0.66, 6.38) | 2.13 (0.68, 6.68) | 1.30 (0.38, 4.46) |
| 60 days | 2.59 (1.07, 6.24) | 2.61 (1.07, 6.37) | 1.23 (0.46, 3.27) |
| 90 days | 2.44 (1.18, 5.07) | 2.48 (1.18, 5.20) | 1.20 (0.52, 2.72) |
| | | | |
| Pneumonia | | | |
| 30 days | 1.80 (1.09, 2.95) | 1.99 (1.21, 3.29) | 0.98 (0.56, 1.71) |
| 60 days | 1.74 (1.13, 2.69) | 1.90 (1.23, 2.96) | 0.87 (0.54, 1.43) |
| 90 days | 2.10 (1.43, 3.07) | 2.30 (1.56, 3.38) | 1.01 (0.65, 1.55) |
| | | | |
| Bowel obstruction | | | |
| 30 days | 2.56 (1.40, 4.66) | 2.86 (1.56, 5.27) | 1.97 (1.01, 3.85) |
| 60 days | 2.58 (1.55, 4.28) | 2.87 (1.71, 4.80) | 2.01 (1.14, 3.53) |
| 90 days | 2.30 (1.45, 3.67) | 2.54 (1.58, 4.08) | 1.79 (1.07, 3.01) |

Model 1 is adjusted for age, sex, race/ethnicity and region of residence. Model 2 is adjusted for comorbidity index, frailty, and number of unique prescription drugs in addition to the variables in the Model 1.