

# Proton Pump Inhibitors and the Risk for Fracture at Specific Sites: Data Mining of the FDA Adverse Event Reporting System

Liwei Wang<sup>1,2,\*</sup>, Mei Li<sup>1</sup>, Yuying Cao<sup>1</sup>, Zhengqi Han<sup>3</sup>, Xueju Wang<sup>4</sup>, Elizabeth J. Atkinson<sup>2</sup>, Hongfang Liu<sup>2,\*</sup>, Shreyasee Amin<sup>2,5,\*</sup>

<sup>1</sup> Department of Medical Informatics, School of Public Health, Jilin University, Changchun 130021, Jilin Province, China.

<sup>2</sup> Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester 55901 MN, U.S.

<sup>3</sup> National Science Library, Chinese Academy of Science, Beijing 100190, China

<sup>4</sup> Department of Pathology, the Third Hospital of Jilin University, Changchun 130033, Jilin province, China

<sup>5</sup> Division of Rheumatology, Mayo Clinic College of Medicine, Rochester 55901 MN, U.S

Liwei Wang and Mei Li are co-first authors.

\*Corresponding author: wang.liwei@mayo.edu

\*Corresponding author: liu.hongfang@mayo.edu

\*Corresponding author: amin.shreyasee@mayo.edu

**Page 2-4 Supplementary Table S1.** Signal detection between any proton pump inhibitor (PPI) and reported fracture adverse events as classified by MedDRA's 8 High Level Terms (HLT) and corresponding 61 Preferred Terms (PT), by overall and gender groups. Bold indicates statistically significant signals.

**Page 5-7 Supplementary Table S2.** Signal detection between each proton pump inhibitor (PPI) and reported fracture adverse events as classified by MedDRA's 8 High Level Terms (HLT) and corresponding 61 Preferred Terms (PT). Bold indicates a statistically significant signal.

**Supplementary Table S1.** Signal detection between any proton pump inhibitor (PPI) and reported fracture adverse events as classified by MedDRA's 8 High Level Terms (HLT) and corresponding 61 Preferred Terms (PT), by overall and gender groups. Bold indicates statistically significant signals.

| Fracture Site   | Overall |                   | Males |                   | Females |                   |
|---|---------|-------------------|-------|-------------------|---------|-------------------|
|   | N       | PRR( $\chi^2$ )   | N     | PRR( $\chi^2$ )   | N       | PRR( $\chi^2$ )   |
| Skull and face fractures                                  | 113     | 1.7(29.5)         | 32    | 1.2(0.9)          | 81      | <b>2.2(44.1)</b>  |
| Skull fractured base                                      | 8       | <b>2.8(7.9)</b>   | 4     | 2.3(2.4)          | 4       | <b>4.2(7.3)</b>   |
| Skull fracture  | 24      | 1.2(0.7)          | 11    | 1.2(0.3)          | 13      | 1.2(0.5)          |
| Facial bones fracture                                     | 81      | 1.8(25.7)         | 17    | 1.0(<0.1)         | 64      | <b>2.4(45.6)</b>  |
| Fractured skull depressed                                 | 0       | —                 | 0     | —                 | 0       | —                 |
| Thoracic cage fractures non-spinal<br>(excl pathological) | 437     | <b>2.5(323.5)</b> | 143   | <b>2.5(104.9)</b> | 291     | <b>2.6(231.5)</b> |
| Sternal fracture  | 22      | 1.9(9.5)          | 8     | <b>2.6(6.5)</b>   | 14      | 1.9(5.3)          |
| Rib fracture  | 423     | <b>2.5(325.4)</b> | 138   | <b>2.5(103.2)</b> | 282     | <b>2.6(234.0)</b> |
| Flail chest   | 2       | 2.5(1.5)          | 1     | 2.7(0.9)          | 1       | 2.3(0.6)          |
| Spinal fractures (excl pathological)                      | 517     | <b>2.2(290.7)</b> | 114   | <b>2.1(53.5)</b>  | 396     | <b>2.3(244.9)</b> |
| Spinal fracture   | 323     | <b>2.3(209.9)</b> | 74    | <b>2.4(53.7)</b>  | 245     | <b>2.4(163.6)</b> |
| Cervical vertebral fracture                               | 50      | 1.8(16.3)         | 16    | 1.5(2.1)          | 34      | <b>2.1(16.9)</b>  |
| Thoracic vertebral fracture                               | 58      | <b>2.6(47.7)</b>  | 7     | <b>1.3(0.5)</b>   | 49      | <b>3.0(52.0)</b>  |
| Lumbar vertebral fracture                                 | 68      | 1.9(27.3)         | 13    | 1.4(1.2)          | 53      | <b>2.2(28.6)</b>  |
| Fractured sacrum  | 43      | <b>3.6(64.0)</b>  | 7     | <b>6.3(21.3)</b>  | 36      | <b>3.4(47.6)</b>  |
| Fractured coccyx  | 13      | 1.2(0.6)          | 3     | 2.0(1.4)          | 10      | 1.1(0.2)          |
| Pelvic fractures  | 200     | <b>2.1(98.4)</b>  | 31    | <b>2.3(18.5)</b>  | 167     | <b>2.1(84.2)</b>  |
| Pelvic fracture   | 160     | 1.9(62.6)         | 22    | <b>2.0(9.7)</b>   | 136     | 1.9(55.5)         |
| Ilium fracture  | 4       | 1.4(0.3)          | 2     | 3.9(3.3)          | 2       | 0.9(<0.1)         |
| Pubis fracture  | 26      | <b>3.8(41.5)</b>  | 4     | <b>6.0(11.5)</b>  | 22      | <b>3.5(31.7)</b>  |

|                                   |      |                   |     |                  |      |                   |
|-----------------------------------|------|-------------------|-----|------------------|------|-------------------|
| Acetabulum fracture               | 14   | <b>3.6(21.1)</b>  | 3   | 1.8(1.0)         | 11   | <b>4.9(25.4)</b>  |
| Fractured ischium                 | 2    | 1.0(<0.1)         | 0   | —                | 2    | 1.5(0.3)          |
| Upper limb fractures              | 768  | 1.8 (249.3 )      | 149 | 1.7(35.4)        | 615  | 1.9(232.4)        |
| Upper Limb fracture               | 282  | 1.7(69.6)         | 48  | 1.5(6.6)         | 234  | 1.8(72.5)         |
| Clavicle fracture                 | 57   | 1.7 (15.1 )       | 19  | 1.7(4.6)         | 37   | 1.8(11.4)         |
| Scapula fracture                  | 14   | <b>2.7 (12.5)</b> | 9   | <b>5.1(21.4)</b> | 5    | 1.5(0.8)          |
| Humerus fracture                  | 114  | <b>2.2(61.4)</b>  | 17  | 1.5(2.4)         | 97   | <b>2.4(67.2)</b>  |
| Forearm fracture                  | 10   | 1.8(3.3)          | 1   | 0.9(<0.1)        | 9    | <b>2.2(5.1)</b>   |
| Radius fracture                   | 65   | <b>2.6(51.6)</b>  | 16  | <b>2.8(15.8)</b> | 49   | <b>2.5(37.4)</b>  |
| Ulna fracture                     | 30   | <b>3.0(32.3)</b>  | 8   | <b>4.3(15.5)</b> | 22   | <b>2.7(19.6)</b>  |
| Wrist fracture                    | 205  | 1.9(78.7)         | 26  | 1.9(9.2)         | 177  | 1.9(72.1)         |
| Hand fracture                     | 100  | 1.9(38.9)         | 22  | 1.4(2.6)         | 77   | <b>2.2(42.6)</b>  |
| Scapulothoracic dissociation      | 0    | —                 | 0   | —                | 0    | —                 |
| Lower limb fractures              | 1714 | 1.5(270.0)        | 320 | 1.6(61.2)        | 1376 | 1.5(231.9)        |
| Lower limb fracture               | 202  | 1.4(24.0)         | 40  | 1.1(0.5)         | 161  | 1.6(30.3)         |
| Hip fracture                      | 497  | 1.7(136.7)        | 92  | 1.6(18.7)        | 402  | 1.8(130.2)        |
| Femoral neck fracture             | 81   | 1.5(12.5)         | 17  | 1.2(0.7)         | 63   | 1.6(14.2)         |
| Femur fracture                    | 454  | 1.3(24.8)         | 61  | 1.7(14.6)        | 390  | 1.3(21.4)         |
| Patella fracture                  | 35   | 1.7(8.2)          | 5   | 1.5(0.7)         | 30   | 1.7(8.5)          |
| Tibia fracture                    | 92   | 1.9(37.8)         | 19  | 1.8(6.5)         | 71   | <b>2.0(31.2)</b>  |
| Fibula fracture                   | 71   | <b>2.2(39.7)</b>  | 15  | 1.9(6.4)         | 54   | <b>2.2(31.9)</b>  |
| Ankle fracture                    | 223  | 1.5(31.1)         | 36  | 1.3(1.9)         | 181  | 1.5(27.7)         |
| Foot fracture                     | 291  | 1.8(97.1)         | 66  | <b>2.5(52.2)</b> | 224  | 1.7(62.5)         |
| Fractures NEC (excl pathological) | 638  | 1.9(277.9)        | 149 | <b>2.0(67.6)</b> | 484  | <b>2.1(233.1)</b> |
| Periprosthetic fracture           | 4    | <b>4.9(9.1)</b>   | 0   | —                | 4    | <b>5.4(10.3)</b>  |
| Fracture displacement             | 18   | <b>4.2(33.4)</b>  | 0   | —                | 18   | <b>4.7(38.6)</b>  |

|  |     |                   |    |                  |     |                   |
|--|-----|-------------------|----|------------------|-----|-------------------|
| Compression fracture                     | 169 | <b>3.7(256.9)</b> | 45 | <b>3.9(75.9)</b> | 124 | <b>3.7(189.7)</b> |
| Bone fragmentation                       | 28  | <b>3.6(41.5)</b>  | 7  | <b>3.2(8.3)</b>  | 21  | <b>4.1(37.1)</b>  |
| Avulsion fracture                        | 5   | <b>2.7(4.5)</b>   | 3  | <b>3.4(4.0)</b>  | 2   | 2.3(1.2)          |
| Jaw fracture                             | 77  | <b>2.5(61.0)</b>  | 27 | <b>2.8(25.2)</b> | 50  | <b>2.5(38.9)</b>  |
| Bone fissure                             | 6   | 1.3(0.3)          | 2  | 1.9(0.8)         | 4   | 1.1(0.1)          |
| Complicated fracture                     | 3   | 3.5(0.1)          | 0  | —                | 3   | <b>6.8(9.8)</b>   |
| Epiphyseal fracture                      | 1   | 3.4(1.3)          | 1  | 6.8(3.3)         | 0   | —                 |
| Fracture                                 | 168 | 1.3(13.9)         | 32 | 1.1(0.3)         | 134 | 1.5(21.4)         |
| Impacted fracture                        | 1   | 2.7(0.9)          | 1  | 6.8(3.3)         | 0   | —                 |
| Multiple fractures                       | 59  | 1.7(15.0)         | 19 | 1.8(5.8)         | 40  | 1.7(10.5)         |
| Open fracture                            | 13  | 1.9(5.1)          | 6  | <b>2.8(5.7)</b>  | 7   | 1.6(1.4)          |
| Stress fracture                          | 116 | 1.9(40.8)         | 19 | <b>3.7(29.6)</b> | 95  | 1.7(24.3)         |
| Torus fracture                           | 1   | 3.4(1.3)          | 0  | —                | 1   | 6.8(3.3)          |
| Traumatic fracture                       | 11  | 1.5(1.9)          | 1  | 0.6(0.2)         | 9   | 1.7(2.5)          |
| Greenstick fracture                      | 0   | —                 | 0  | —                | 0   | —                 |
| Pathological fractures and complications | 277 | <b>2.6(223.3)</b> | 75 | <b>3.2(92.0)</b> | 201 | <b>2.5(147.6)</b> |
| Pathological fracture                    | 188 | <b>3.1(218.6)</b> | 55 | <b>3.6(83.0)</b> | 133 | <b>3.0(147.7)</b> |
| Pseudarthrosis                           | 8   | <b>2.3(5.3)</b>   | 4  | <b>3.6(5.9)</b>  | 4   | 1.9(1.6)          |
| Osteoporotic fracture                    | 31  | <b>2.3(19.7)</b>  | 8  | <b>2.5(6.1)</b>  | 23  | <b>2.3(15.0)</b>  |
| Fracture nonunion                        | 39  | <b>2.2(21.8)</b>  | 6  | <b>3.7(9.2)</b>  | 32  | <b>2.0(14.1)</b>  |
| Fracture malunion                        | 2   | 0.8(0.1)          | 1  | 13.5(5.8)        | 1   | 0.5(0.6)          |
| Fracture delayed union                   | 20  | 1.7(5.1)          | 2  | 2.3(1.2)         | 18  | 1.7(4.6)          |
| Synostosis                               | 1   | 0.5(0.6)          | 0  | —                | 1   | 1.5(0.2)          |

**Supplementary Table S2.** Signal detection between each proton pump inhibitor (PPI) and reported fracture adverse events as classified by MedDRA's 8 High Level Terms (HLT) and corresponding 61 Preferred Terms (PT). Bold indicates a statistically significant signal.

|  | Omeprazole |                   | Lansoprazole |                  | Pantoprazole |                   | Rabeprazole |                  | Esomeprazole |                   |
|--|------------|-------------------|--------------|------------------|--------------|-------------------|-------------|------------------|--------------|-------------------|
|  | Reports    | PRR( $\chi^2$ )   | Reports      | PRR( $\chi^2$ )  | Reports      | PRR( $\chi^2$ )   | Reports     | PRR( $\chi^2$ )  | Reports      | PRR( $\chi^2$ )   |
| Skull and face fractures                               | 47         | 1.9(21.8)         | 17           | 1.4(2.0)         | <b>25</b>    | <b>2.1(13.2)</b>  | <b>14</b>   | <b>4.6(38.7)</b> | 29           | 1.4(3.8)          |
| Skull fractured base                                   | <b>4</b>   | <b>3.9(7.7)</b>   | 0            | —                | 0            | —                 | 0           | —                | <b>4</b>     | <b>4.6(10.4)</b>  |
| Skull fracture   | 11         | 1.6(2.1)          | 3            | 0.8(0.1)         | 3            | 0.8(0.1)          | 1           | 1.1(<0.1)        | 8            | 1.3(0.7)          |
| Facial bones fracture                                  | 32         | 1.9(14.7)         | 14           | 1.7(4.1)         | <b>22</b>    | <b>2.7(22.2)</b>  | <b>13</b>   | <b>6.3(56.4)</b> | 17           | 1.2(0.7)          |
| Fractured skull depressed                              | 0          | —                 | 0            | —                | 0            | —                 | 0           | —                | 0            | —                 |
| Thoracic cage fractures non-spinal (excl pathological) | <b>181</b> | <b>2.1(122.8)</b> | <b>75</b>    | <b>2.2(50.5)</b> | <b>101</b>   | <b>3.0(128.8)</b> | <b>19</b>   | <b>2.2(12.3)</b> | <b>81</b>    | <b>2.4(61.7)</b>  |
| Sternal fracture                                       | <b>10</b>  | <b>2.5(8.6)</b>   | 2            | 1.0(<0.1)        | <b>5</b>     | <b>2.4(4.1)</b>   | 0           | —                | 6            | 1.8(1.9)          |
| Rib fracture   | <b>175</b> | <b>2.8(190.5)</b> | <b>73</b>    | <b>2.3(51.8)</b> | <b>98</b>    | <b>3.0(129.4)</b> | <b>19</b>   | <b>2.3(13.9)</b> | <b>135</b>   | <b>2.6(121.7)</b> |
| Flail chest  | 0          | —                 | 1            | 6.9(4.6)         | 0            | —                 | 0           | —                | <b>2</b>     | 8.8(11.7)         |
| Spinal fractures (excl pathological)                   | <b>201</b> | <b>2.3(143.9)</b> | 68           | 1.5(12.9)        | <b>93</b>    | <b>2.1(51.0)</b>  | <b>27</b>   | <b>2.4(21.7)</b> | <b>174</b>   | <b>2.4(135.3)</b> |
| Spinal fracture  | <b>114</b> | <b>2.2(72.3)</b>  | 44           | 1.7(12.1)        | <b>56</b>    | <b>2.1(32.0)</b>  | <b>21</b>   | <b>3.1(30.3)</b> | <b>116</b>   | <b>2.7(118.5)</b> |
| Cervical vertebral fracture                            | 18         | 1.8(6.2)          | 7            | 1.4(0.8)         | 8            | 1.6(1.6)          | <b>4</b>    | <b>3.1(5.7)</b>  | <b>17</b>    | <b>2.0(8.7)</b>   |
| Thoracic vertebral fracture                            | <b>21</b>  | <b>2.5(17.9)</b>  | <b>9</b>     | <b>2.1(5.1)</b>  | <b>15</b>    | <b>3.5(25.7)</b>  | 1           | 0.9(<0.1)        | <b>17</b>    | <b>2.4(13.3)</b>  |
| Lumbar vertebral fracture                              | <b>33</b>  | <b>2.6(31.3)</b>  | 4            | 0.6(1.0)         | <b>17</b>    | <b>2.6(16.5)</b>  | 1           | 0.6(0.3)         | 17           | 1.6(3.5)          |
| Fractured sacrum                                       | <b>17</b>  | <b>3.7(30.3)</b>  | <b>6</b>     | <b>2.5(5.2)</b>  | <b>8</b>     | <b>3.3(12.2)</b>  | 1           | 1.6(0.2)         | <b>17</b>    | <b>4.4(41.1)</b>  |
| Fractured coccyx                                       | 6          | 1.6(1.4)          | 3            | 1.6(0.7)         | 2            | 1.1(<0.1)         | 1           | 2.1(0.6)         | 4            | 1.3(0.3)          |
| Pelvic fractures                                       | <b>88</b>  | <b>2.5(76.8)</b>  | 20           | 1.1(0.2)         | 40           | 2.2(26.1)         | <b>20</b>   | <b>4.4(52.0)</b> | 59           | 1.9(28.2)         |
| Pelvic fracture  | <b>65</b>  | <b>2.2(38.5)</b>  | 18           | 1.2(0.5)         | 30           | 1.9(13.2)         | <b>17</b>   | <b>4.4(43.6)</b> | <b>51</b>    | <b>2.0(24.9)</b>  |
| Ilium fracture   | 3          | 3.0(3.6)          | 0            | —                | 1            | 1.9(0.4)          | 1           | 7.5(5.6)         | 1            | 1.1(<0.1)         |
| Pubis fracture   | <b>12</b>  | <b>4.5(55.7)</b>  | 2            | 1.4(0.2)         | <b>6</b>     | <b>4.3(14.3)</b>  | 2           | 5.5(7.3)         | 5            | 2.1(2.9)          |
| Acetabulum fracture                                    | <b>9</b>   | <b>6.4(35.3)</b>  | 0            | —                | <b>5</b>     | <b>6.6(22.0)</b>  | 1           | 5.0(3.1)         | 3            | 2.3(2.1)          |

|                                   | Omeprazole |                   | Lansoprazole |                   | Pantoprazole |                   | Rabeprazole |                  | Esomeprazole |                   |
|-----------------------------------|------------|-------------------|--------------|-------------------|--------------|-------------------|-------------|------------------|--------------|-------------------|
|                                   | Reports    | PRR( $\chi^2$ )   | Reports      | PRR( $\chi^2$ )   | Reports      | PRR( $\chi^2$ )   | Reports     | PRR( $\chi^2$ )  | Reports      | PRR( $\chi^2$ )   |
| Fractured ischium                 | 1          | 1.4(0.1)          | 0            | —                 | 0            | —                 | 0           | —                | 1            | 1.7(0.3)          |
| Upper limb fractures              | 295        | 1.9(126.3)        | 109          | 1.4(12.8)         | <b>157</b>   | <b>2.0(77.0)</b>  | 37          | 1.9(14.8)        | 255          | 1.9(120.5)        |
| Upper Limb fracture               | 102        | 1.7(27.5)         | 30           | 1.0(<0.1)         | 45           | 1.5(6.2)          | 9           | 1.2(0.2)         | <b>118</b>   | <b>2.4(88.1)</b>  |
| Clavicle fracture                 | 22         | 1.8(8.0)          | 7            | 1.2(0.1)          | <b>17</b>    | <b>2.8(19.0)</b>  | 3           | 1.9(1.3)         | 16           | 1.6(3.3)          |
| Scapula fracture                  | <b>5</b>   | <b>2.6(4.5)</b>   | <b>5</b>     | <b>5.2(16.0)</b>  | 2            | 2.0(0.9)          | 2           | 7.9(11.8)        | 2            | 1.2(0.1)          |
| Humerus fracture                  | <b>46</b>  | <b>2.4(34.9)</b>  | 18           | 1.8(6.7)          | <b>35</b>    | <b>3.6(61.9)</b>  | 7           | <b>2.8(7.9)</b>  | 26           | 1.6(5.3)          |
| Forearm fracture                  | <b>5</b>   | <b>2.6(4.5)</b>   | 0            | —                 | <b>5</b>     | <b>5.1(15.5)</b>  | 0           | —                | 2            | 1.2(0.1)          |
| Radius fracture                   | <b>28</b>  | <b>3.0(34.1)</b>  | <b>10</b>    | <b>2.1(5.4)</b>   | <b>17</b>    | <b>3.5(29.0)</b>  | 7           | <b>5.7(26.4)</b> | 11           | 1.3(0.9)          |
| Ulna fracture                     | <b>11</b>  | <b>2.9(12.5)</b>  | 7            | <b>3.6(12.8)</b>  | <b>6</b>     | <b>3.0(7.8)</b>   | 0           | —                | <b>9</b>     | <b>2.8(9.7)</b>   |
| Wrist fracture                    | <b>82</b>  | <b>2.1(45.8)</b>  | 33           | 1.7(8.9)          | 33           | 1.6(8.2)          | <b>11</b>   | <b>2.2(7.0)</b>  | <b>69</b>    | <b>2.1(39.0)</b>  |
| Hand fracture                     | <b>39</b>  | <b>2.1(20.4)</b>  | 15           | 1.6(3.1)          | 19           | 1.9(8.7)          | 3           | 1.1(0.1)         | <b>37</b>    | <b>2.3(27.3)</b>  |
| Scapulothoracic dissociation      | 0          | —                 | 0            | —                 | 0            | —                 | 0           | —                | 0            | —                 |
| Lower limb fractures              | 633        | 1.6(124.2)        | 287          | 1.4(34.4)         | 338          | 1.6(81.9)         | 78          | 1.5(12.8)        | 558          | 1.6(137.3)        |
| Lower limb fracture               | 67         | 1.3(5.3)          | 25           | 1.0(<0.1)         | 38           | 1.5(5.8)          | 8           | 1.2(0.4)         | 80           | 1.9(33.7)         |
| Hip fracture                      | 181        | 1.7(55.4)         | 83           | 1.6(18.1)         | <b>116</b>   | <b>2.2(73.8)</b>  | <b>27</b>   | <b>2.0(13.8)</b> | 147          | 1.7(39.9)         |
| Femoral neck fracture             | 29         | 1.5(4.8)          | <b>23</b>    | <b>2.4(18.6)</b>  | 18           | 1.8(6.8)          | 1           | 0.4(0.9)         | 20           | 1.2(0.9)          |
| Femur fracture                    | 205        | 1.6(49.2)         | 59           | 0.9(0.3)          | 86           | 1.3(7.3)          | 17          | 1.1(<0.1)        | 138          | 1.3(9.7)          |
| Patella fracture                  | 13         | 1.7(3.7)          | 5            | 1.3(0.4)          | 4            | 1.0(<0.1)         | <b>5</b>    | <b>5.2(16.5)</b> | 11           | 1.7(3.2)          |
| Tibia fracture                    | <b>40</b>  | <b>2.4(29.5)</b>  | <b>25</b>    | <b>2.9(30.9)</b>  | 15           | 1.7(4.2)          | 3           | 1.3(0.3)         | 18           | 1.2(0.8)          |
| Fibula fracture                   | <b>28</b>  | <b>2.4(20.7)</b>  | <b>13</b>    | <b>2.2(7.9)</b>   | <b>17</b>    | <b>2.8(18.9)</b>  | <b>6</b>    | <b>3.9(12.7)</b> | 16           | 1.6(3.3)          |
| Ankle fracture                    | 80         | 1.5(12.1)         | 47           | 1.7(14.8)         | 34           | 1.2(1.4)          | 10          | 1.4(1.4)         | 84           | 1.9(32.8)         |
| Foot fracture                     | 89         | 1.5(15.9)         | 48           | 1.7(12.3)         | <b>62</b>    | <b>2.1(35.1)</b>  | <b>18</b>   | <b>2.4(14.9)</b> | <b>118</b>   | <b>2.4(88.1)</b>  |
| Fractures NEC (excl pathological) | <b>239</b> | <b>2.1(122.8)</b> | <b>142</b>   | <b>2.4(116.8)</b> | <b>139</b>   | <b>2.3(102.6)</b> | <b>38</b>   | <b>2.5(34.4)</b> | <b>207</b>   | <b>2.1(117.1)</b> |
| Periprosthetic fracture           | 2          | 6.2(7.6)          | 0            | —                 | 2            | 12.4(18.2)        | 0           | —                | 0            | —                 |

|  | Omeprazole |                   | Lansoprazole |                    | Pantoprazole |                   | Rabeprazole |                  | Esomeprazole |                  |
|--|------------|-------------------|--------------|--------------------|--------------|-------------------|-------------|------------------|--------------|------------------|
|  | Reports    | PRR( $\chi^2$ )   | Reports      | PRR( $\chi^2$ )    | Reports      | PRR( $\chi^2$ )   | Reports     | PRR( $\chi^2$ )  | Reports      | PRR( $\chi^2$ )  |
| Fracture displacement                    | <b>10</b>  | <b>6.1(37.2)</b>  | <b>3</b>     | <b>3.4(4.8)</b>    | <b>4</b>     | <b>4.5(10.2)</b>  | 2           | 8.8(13.4)        | <b>7</b>     | <b>4.9(19.9)</b> |
| Compression fracture                     | <b>65</b>  | <b>3.6(112.6)</b> | <b>35</b>    | <b>3.8(69.2)</b>   | <b>48</b>    | <b>5.2(152.7)</b> | <b>13</b>   | <b>5.4(46.0)</b> | <b>53</b>    | <b>3.5(87.1)</b> |
| Bone fragmentation                       | <b>12</b>  | <b>4.0(24.7)</b>  | <b>15</b>    | <b>10.5(114.1)</b> | <b>8</b>     | <b>5.2(25.2)</b>  | 1           | 2.5(0.9)         | <b>10</b>    | <b>3.9(20.3)</b> |
| Avulsion fracture                        | <b>4</b>   | <b>6.2(15.2)</b>  | 1            | 2.8(1.2)           | 1            | 2.8(1.1)          | 0           | —                | 1            | 1.7(0.3)         |
| Jaw fracture                             | <b>25</b>  | <b>2.2(15.5)</b>  | <b>28</b>    | <b>5.0(85.7)</b>   | <b>23</b>    | <b>4.0(49.5)</b>  | 2           | 1.3(0.2)         | <b>21</b>    | <b>2.2(13.1)</b> |
| Bone fissure                             | 2          | 1.2(0.1)          | 0            | —                  | 1            | 1.2(<0.1)         | 2           | 9.5(14.9)        | 1            | 0.7(0.1)         |
| Complicated fracture                     | <b>3</b>   | <b>9.3(18.1)</b>  | 1            | 5.5(3.4)           | 1            | 5.4(3.3)          | 0           | —                | 1            | 3.2(1.4)         |
| Epiphyseal fracture                      | 0          | —                 | 0            | —                  | 0            | —                 | 0           | —                | 1            | 12.1(8.2)        |
| Fracture                                 | 58         | 1.3(4.1)          | 28           | 1.3(1.6)           | 29           | 1.3(1.8)          | 8           | 1.4(1.0)         | 60           | 1.6(14.0)        |
| Impacted fracture                        | 1          | 8.1(5.2)          | 0            | —                  | 0            | —                 | 0           | —                | 0            | —                |
| Multiple fractures                       | 20         | 1.6(4.2)          | <b>16</b>    | <b>2.6(14.9)</b>   | 9            | 1.4(1.0)          | 2           | 1.2(0.1)         | <b>21</b>    | <b>2.0(10.2)</b> |
| Open fracture                            | 2          | 0.8(0.1)          | 1            | 0.8(<0.1)          | <b>5</b>     | <b>4.1(11.0)</b>  | 0           | —                | <b>6</b>     | <b>3.0(7.4)</b>  |
| Stress fracture                          | <b>46</b>  | <b>2.0(23.3)</b>  | <b>26</b>    | <b>2.3(18.6)</b>   | 21           | 1.8(7.4)          | <b>10</b>   | <b>3.4(17.0)</b> | <b>41</b>    | <b>2.2(24.8)</b> |
| Torus fracture                           | 0          | —                 | 1            | 20.6(14.9)         | 0            | —                 | 0           | —                | 0            | —                |
| Traumatic fracture                       | 3          | 1.2(0.1)          | <b>5</b>     | <b>4.0(10.9)</b>   | 1            | 0.8(0.1)          | 1           | 3.1(1.4)         | 1            | 0.5(0.6)         |
| Greenstick fracture                      | 0          | —                 | 0            | —                  | 0            | —                 | 0           | —                | 0            | —                |
| Pathological fractures and complications | <b>122</b> | <b>3.1(157.6)</b> | <b>42</b>    | <b>2.0(21.9)</b>   | <b>62</b>    | <b>3.0(79.2)</b>  | <b>15</b>   | <b>2.8(17.7)</b> | <b>81</b>    | <b>2.4(61.7)</b> |
| Pathological fracture                    | <b>86</b>  | <b>3.8(161.1)</b> | <b>29</b>    | <b>2.4(24.1)</b>   | <b>48</b>    | <b>4.0(104.7)</b> | <b>7</b>    | <b>2.3(5.0)</b>  | <b>54</b>    | <b>2.8(57.1)</b> |
| Pseudarthrosis                           | <b>4</b>   | <b>3.2(5.7)</b>   | <b>3</b>     | <b>4.8(8.7)</b>    | 1            | 1.5(0.2)          | 0           | —                | 0            | —                |
| Osteoporotic fracture                    | <b>11</b>  | <b>2.2(6.9)</b>   | 2            | 0.8(0.1)           | 5            | 1.9(2.2)          | 2           | 3.1(2.8)         | <b>12</b>    | <b>2.9(14.2)</b> |
| Fracture nonunion                        | <b>15</b>  | <b>2.3(10.4)</b>  | <b>7</b>     | <b>2.1(4.0)</b>    | 7            | 2.1(3.8)          | <b>4</b>    | <b>4.7(11.6)</b> | <b>14</b>    | <b>2.6(12.7)</b> |
| Fracture malunion                        | 0          | —                 | 0            | —                  | 1            | 2.4(0.8)          | 0           | —                | 1            | 1.5(0.1)         |
| Fracture delayed union                   | 7          | 1.6(1.7)          | 1            | 0.5(0.6)           | 2            | 0.9(<0.1)         | <b>5</b>    | <b>9.3(36.1)</b> | <b>9</b>     | <b>2.6(8.2)</b>  |
| Synostosis                               | 0          | —                 | 1            | 2.8(1.2)           | 0            | —                 | 0           | —                | 0            | —                |

\* Dexlansoprazole is not in table due to insufficient reports.