**Supplemental table 1: Association of acid suppressants and onset of *Clostridioides Difficile* infection when antibiotics are separated into 2 groups (specific and non-specific) (Conditional regression analysis)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Reference** | **Multivariate OR (95% CI)\*** | **P value** |
| Antibiotics |  |  |  |
| Specific antibiotics # | none | 4.40 (3.70-4.41) | P<0.0001 |
| Non-specific antibiotics | none | 3.44 (1.15-1.50) | P<0.0001 |
| Acid inhibitory drugs |  |  |  |
| H2-blockers | none | 1.17 (1.04-1.32) | 0.009 |
| Proton pump inhibitors | none | 1.34 (1.24-1.46) | P<0.0001 |
| Vonoprazan | none | 1.41 (1.20-1.66) | P<0.0001 |

#: specific antibiotics comprise quinolones and cephalosporins. \*: adjusted by antibiotics and acid inhibitory drugs.

**Supplemental table 2: Interaction between antibiotics and acid inhibitory drugs for onset of *Clostridioides Difficile* infection (Conditional regression analysis)**

|  |  |  |
| --- | --- | --- |
| **Parameters** | **Multivariate OR (95% CI)\*** | **P value** |
| Antibiotics | 3.81 (3.40 - 4.27) | <0.0001 |
| Acid inhibitory drugs | 1.26 (1.11 - 1.44) | 0.0005 |
| Interaction | 1.05 (0.895 - 1.23) | 0.56 |

\*: adjusted by antibiotics, acid inhibitory drugs, and interaction term.

**Supplemental table 3: Relative associations of acid suppressants with onset of *Clostridioides Difficile* infection in reference to proton pump inhibitors when acid suppressant exposure is defined as any duration of administration (Conditional regression analysis)**

|  |  |  |
| --- | --- | --- |
| **Acid inhibitory drugs** | **Multivariate\* OR (95% CI)** | **Multivariate\* OR (95% CI)** |
| None | 0.75 (0.69 - 0.81) | 0.75 (0.69 - 0.81) |
| H2-receptor antagonists | 0.88 (0.78 - 0.99) | 0.88 (0.78 - 0.99) |
| Proton pump inhibitors | 1.0 (ref) | 1.0 (ref) |
| Vonoprazan | 1.05 (0.90 - 1.23) | - |
| Vonoprazan 10mg | - | 1.08 (0.88 - 1.33) |
| Vonoprazan 20mg | - | 1.01 (0.81 - 1.27) |

\*: adjusted by antibiotics and acid inhibitory drugs. CI: confident interval, OR: odds ratio

**Supplemental Table 4: Related factors associated with the onset of *Clostridioides difficile* infection (unconditional regression analyses)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | **Reference** | **Univariate** | |  | **Multivariate\*** | |
| **OR (95% CI)** | **P value** |  | **OR (95% CI)** | **P value** |
| Antibiotics: yes | no | 3.55 (3.29 – 3.83) | <0.0001 |  | 3.51 (3.25 – 3.79) | <0.0001 |
| ICU administration: yes | no | 1.04 (0.90 – 1.21) | 0.59 |  | - | - |
| Acid inhibitory drugs |  |  |  |  |  |  |
| H2-blockers | none | 0.99 (0.87 – 1.13) | 0.91 |  | 1.14 (0.99 – 1.31) | 0.07 |
| Proton pump inhibitors | none | 1.31 (1.22 – 1.41) | <0.0001 |  | 1.31 (1.21 – 1.41) | <0.0001 |
| Vonoprazan | none | 1.28 (1.10 – 1.48) | 0.0009 |  | 1.38 (1.18 – 1.61) | <0.0001 |
| Trend | None: 0  H2RA: 1  PPI: 2  Vonoprazan: 3 | 1.16 (1.12 – 1.20) | <0.0001 |  | 1.13 (1.10 – 1.17) | <0.0001 |

\*: adjusted by age, antibiotics, and acid inhibitory drugs. ICU: intensive care unit, CI: confident interval, H2RAs: H2 receptor antagonists, OR: odds ratio, PPIs: proton pump inhibitors

**Supplemental Table 5: Odds ratio of the onset of *Clostridioides difficile* infection in patients treated with various acid inhibitory drugs, with reference to proton pump inhibitors (Unconditional regression analysis)**

|  |  |  |
| --- | --- | --- |
| **Acid inhibitory drugs** | **Multivariate\* OR (95% CI)** | **Multivariate\* OR (95% CI)** |
| None | 0.77 (0.71 – 0.83) | 0.77 (0.71 – 0.83) |
| H2-receptor antagonists | 0.87 (0.76 – 1.01) | 0.87 (0.76 – 1.01) |
| Proton pump inhibitors | 1.0 (ref) | 1.0 (ref) |
| Vonoprazan | 1.05 (0.90 – 1.23) | - |
| Vonoprazan 10mg | - | 1.12 (0.91 – 1.38) |
| Vonoprazan 20mg | - | 0.98 (0.78 – 1.23) |

\*: adjusted by age, antibiotics, and acid inhibitory drugs. CI: confident interval, OR: odds ratio