**Supplementary Appendix**

**Title**

Higher risk of hospitalized infection, cardiovascular disease, and fracture in patients with rheumatoid arthritis determined using the Japanese health insurance database

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**Online supplementary Table S1: DMARDs approved by 2013 in Japan.**

|  |  |
| --- | --- |
| Synthetic DMARDs | methotrexate, salazosulfapyridine, tacrolimus hydrate, bucillamine, leflunomide, iguratimod, tofacitinib citrate, mizoribine, actarit, lobenzarit disodium, sodium aurothiomalate, penicillamine, auranofin |
| Biological DMARDs | infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, tocilizumab, abatacept |

**Online supplementary Table S2: Comparison of baseline data between patients with and without hospitalized infection.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | With HI  (n=1,157) | Without HI  (n=39,115) | *P* valuee |
| Median age, yearsa  Female, %  Diabetes mellitus, %  Chronic kidney diseases, %  Chronic pulmonary disease, %  Oral corticosteroidb use, %  Dose of oral corticosteroidsa, c, mg/day  Hospitalized infection at baselined, % | 52.0 (43.0–59.0)  72.5  8.0  6.5  14.7  17.5  5.0 (3.0–10.0)  1.6 | 52.0 (42.0–60.0)  75.7  3.9  1.4  8.0  6.4  5.0 (3.0–7.0)  0.5 | <0.001  0.012  <0.001  <0.001  <0.001  <0.001  0.031  <0.001 |

HI: hospitalized infection.

aData are presented as median values (interquartile range) unless stated otherwise.

bEach medication use was counted when patients had at least one prescription of these drugs during the index month or the following two months.

cOral corticosteroid dose was converted to the equivalent prednisolone dosage.

dHospitalized infection was counted during 6months before the start of the observation of each patient.

eThe Mann-Whiteney U test was used for continuous measures, and the chi-square test for categorical measures to calculate p values between the two groups.

**Online supplementary Table S3: Comparison of baseline data between patients with and without CVD or stroke.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | With CVD  or stroke  (n=384) | Without CVD  or stroke  (n=39,888) | *P* valuee |
| Median age, yearsa  Female, %  Diabetes mellitus, %  Chronic kidney diseases, %  Hypertension, %  Dyslipidaemia, %  Atrial fibrillation, %  Oral corticosteroidb use, %  Dose of oral corticosteroidsa, c, mg/day  CVD or stroke at baselined, % | 59.0 (52.0–64.0)  57.6  15.4  9.6  36.5  25.6  1.6  13.8  5.0 (3.0–10.0)  5.2 | 52.0 (42.0–60.0)  75.8  3.9  1.8  14.2  10.8  0.4  6.7  5.0 (3.0–7.5)  0.2 | <0.001  <0.001  <0.001  <0.001  <0.001  <0.001  <0.001  <0.001  0.323  <0.001 |

CVD: cardiovascular disease.

aData are presented as median values (interquartile range) unless stated otherwise.

bEach medication use was counted when patients had at least one prescription of these drugs during the index month or the following two months.

cOral corticosteroid dose was converted to the equivalent prednisolone dosage.

dCVD or stroke was counted during 6months before the start of the observation of each patient.

eThe Mann-Whiteney U test was used for continuous measures, and the chi-square test for categorical measures to calculate p values between the two groups.

**Online supplementary Table S4: Comparison of baseline data between patients with and without CVD.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | With CVD  (n=248) | Without CVD  (n=40,024) | *P* valuee |
| Median age, yearsa  Female, %  Diabetes mellitus, %  Chronic kidney diseases, %  Hypertension, %  Dyslipidaemia, %  Oral corticosteroidb use, %  Dose of oral corticosteroidsa, c, mg/day  CVD at baselined, % | 59.0 (52.0–64.0)  53.2  18.1  12.1  41.5  31.0  16.9  5.0 (3.0–10.0)  4.8 | 52.0 (42.0–60.0)  75.8  3.9  1.8  14.2  10.8  6.7  5.0 (3.0–7.5)  0.1 | <0.001  <0.001  <0.001  <0.001  <0.001  <0.001  <0.001  0.338  <0.001 |

CVD: cardiovascular disease.

aData are presented as median values (interquartile range) unless stated otherwise.

bEach medication use was counted when patients had at least one prescription of these drugs during the index month or the following two months.

cOral corticosteroid dose was converted to the equivalent prednisolone dosage.

dCVD was counted during 6months before the start of the observation of each patient.

eThe Mann-Whiteney U test was used for continuous measures, and the chi-square test for categorical measures to calculate p values between the two groups.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | With stroke  (n=384) | Without stroke  (n=39,888) | *P* valuee |
| Median age, yearsa  Female, %  Diabetes mellitus, %  Chronic kidney diseases, %  Hypertension, %  Dyslipidaemia, %  Atrial fibrillation, %  Oral corticosteroidb use, %  Dose of oral corticosteroidsa, c, mg/day  Stroke at baselined, % | 59.5 (52.0–65.3)  73.0  11.0  5.8  30.5  17.5  1.3  7  .8  5.0 (3.0–8.1)  4.5 | 52.0 (42.0–60.0)  75.7  4.0  1.9  14.3  10.9  0.4  6.7  5.0 (3.0–7.5)  0.1 | <0.001  <0.001  <0.001  <0.001  <0.001  0.009  0.057  0.599  0.636  <0.001 |

**Online supplementary Table S5: Comparison of baseline data between patients with and without stroke.**

aData are presented as median values (interquartile range) unless stated otherwise.

bEach medication use was counted when patients had at least one prescription of these drugs during the index month or the following two months.

cOral corticosteroid dose was converted to the equivalent prednisolone dosage.

dStroke was counted during 6months before the start of the observation of each patient.

eThe Mann-Whiteney U test was used for continuous measures, and the chi-square test for categorical measures to calculate p values between the two groups.

**Online supplementary Table S6: Comparison of baseline data between patients with and without fracture.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | With fracture  (n=436) | Without fracture  (n=39,836) | *P* valuee |
| Median age, yearsa  Female, %  Diabetes mellitus, %  Chronic kidney diseases, %  Oral corticosteroidb use, %  Dose of oral corticosteroidsa, c, mg/day  Fracture at baselined, % | 54.0 (44.0–61.0)  89.9  11.5  5.7  23.9  5.0 (4.3–10.0)  28.7 | 52.0 (42.0–60.0)  75.6  3.9  1.9  6.5  5.0 (3.0–7.5)  0.1 | <0.001  <0.001  <0.001  <0.001  <0.001  0.019  <0.001 |

aData are presented as median values (interquartile range) unless stated otherwise.

bEach medication use was counted when patients had at least one prescription of these drugs during the index month or the following two months.

cOral corticosteroid dose was converted to the equivalent prednisolone dosage.

dFracture or stroke was counted during 6months before the start of the observation of each patient.

eThe Mann-Whiteney U test was used for continuous measures, and the chi-square test for categorical measures to calculate p values between the two groups.

**Online supplementary Table S7: Incidence rates of complications in the corticosteroid non-use group.**

(a) Hospitalized infection

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| RA group (9,306.67PY) | | Non-RA group (83,416.17PY) | | Crude IRR (95% CI) |
| N | IRa (95% CI) | n | IRa (95% CI) |
| 167 | 17.9 (15.4–20.8) | 809 | 9.70 (9.05–10.4) | 1.85 (1.57–2.19) |

(b) CVD or stroke

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| RA group (9,210.75PY) | | Non-RA group (83,216.67PY) | | Crude IRR (95% CI) |
| N | IRa (95% CI) | n | IRa (95% CI) |
| 49 | 5.32 (3.98–6.97) | 357 | 4.29 (3.86–4.75) | 1.24 (0.92–1.67) |

(c) Fracture

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| RA group (9,207.58PY) | | Non-RA group (83,168.67PY) | | Crude IRR (95% CI) |
| N | IRa (95% CI) | n | IRa (95% CI) |
| 71 | 7.71 (6.07–9.67) | 271 | 3.26 (2.89–3.66) | 2.37 (1.82–3.07) |

CI: confidence interval; IR: incidence rate; IRR: incidence rate ratio; PY: patient-year.

aIncidence rate of complications are shown per 1000 patient-years.

**Online supplementary Table S8: Incidence rates of complications in the corticosteroid ever use group.**

(a) Hospitalized infection

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| RA group (9,109.08PY) | | Non-RA group (7,759.33PY) | | Crude IRR (95% CI) |
| N | IRa (95% CI) | n | IRa (95% CI) |
| 279 | 30.6 (27.2–34.4) | 85 | 11.0 (8.81–13.5) | 2.80 (2.19–3.56) |

(b) CVD or stroke

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| RA group (9,205.00PY) | | Non-RA group (7,958.83PY) | | Crude IRR (95% CI) |
| N | IRa (95% CI) | n | IRa (95% CI) |
| 76 | 8.26 (6.55–10.3) | 23 | 2.89 (1.88–4.26) | 2.86 (1.79–4.55) |

(c) Fracture

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| RA group (9,208.17PY) | | Non-RA group (8,006.83PY) | | Crude IRR (95% CI) |
| N | IRa (95% CI) | n | IRa (95% CI) |
| 87 | 13.5 (11.3–16.0) | 13 | 2.12 (1.28–3.32) | 6.34 (3.82–10.5) |

IR: incidence rate; IRR: incidence rate ratio; PY: patient-year.

aIncidence rate of complications are shown per 1000 patient-years.