**Supplementary Appendix**

**Title**

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

**Authors**

Shoko Kasai1; Ryoko Sakai2; Ryuji Koike1; Hitoshi Kohsaka1; Nobuyuki Miyasaka3; Masayoshi Harigai2

**Affiliations**

1Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

2Division of Epidemiology and Pharmacoepidemiology of Rheumatic Diseases, Department of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan

3Tokyo Medical and Dental University, Tokyo, Japan

**Corresponding author:** Masayoshi Harigai,

Division of Epidemiology and Pharmacoepidemiology of Rheumatic Diseases,

Institute of Rheumatology, Tokyo Women’s Medical University,

10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan

TEL: +81-3-3353-8112 ext. 34325; FAX: +81-3-5269-1711, E-mail address: harigai.masayoshi@twmu.ac.jp

**Contents**

Online supplementary Table S1, DMARDs approved by 2013

Online supplementary Table S2, Univariate analysis of hospitalized infection

Online supplementary Table S3, Univariate analysis of CVD or stroke

Online supplementary Table S4, Univariate analysis of CVD

Online supplementary Table S5, Univariate analysis of stroke

Online supplementary Table S6, Univariate analysis of fracture

Online supplementary Table S7, Incidence rates of complications in the corticosteroid non-use group

Online supplementary Table S8, Incidence rates of complications in the corticosteroid ever use group

**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, yearsaFemale, %Diabetes mellitus, %Chronic kidney diseases, %Chronic pulmonary disease, %Oral corticosteroidb use, %Dose of oral corticosteroidsa, c, mg/dayHospitalized infection at baselined, % | 52.0 (43.0–59.0)72.58.06.514.717.55.0 (3.0–10.0)1.6 | 52.0 (42.0–60.0)75.73.91.48.06.45.0 (3.0–7.0)0.5 | <0.0010.012<0.001<0.001<0.001<0.0010.031<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, yearsaFemale, %Diabetes mellitus, %Chronic kidney diseases, %Hypertension, %Dyslipidaemia, %Atrial fibrillation, %Oral corticosteroidb use, %Dose of oral corticosteroidsa, c, mg/dayCVD or stroke at baselined, % | 59.0 (52.0–64.0)57.615.49.636.525.61.613.85.0 (3.0–10.0)5.2 | 52.0 (42.0–60.0)75.83.91.814.210.80.46.75.0 (3.0–7.5)0.2 | <0.001<0.001<0.001<0.001<0.001<0.001<0.001<0.0010.323<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, yearsaFemale, %Diabetes mellitus, %Chronic kidney diseases, %Hypertension, %Dyslipidaemia, %Oral corticosteroidb use, %Dose of oral corticosteroidsa, c, mg/dayCVD at baselined, % | 59.0 (52.0–64.0)53.218.112.141.531.016.95.0 (3.0–10.0)4.8 | 52.0 (42.0–60.0)75.83.91.814.210.86.75.0 (3.0–7.5)0.1 | <0.001<0.001<0.001<0.001<0.001<0.001<0.0010.338<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, yearsaFemale, %Diabetes mellitus, %Chronic kidney diseases, %Hypertension, %Dyslipidaemia, %Atrial fibrillation, %Oral corticosteroidb use, %Dose of oral corticosteroidsa, c, mg/dayStroke at baselined, % | 59.5 (52.0–65.3)73.011.05.830.517.51.37.85.0 (3.0–8.1)4.5 | 52.0 (42.0–60.0)75.74.01.914.310.90.46.75.0 (3.0–7.5)0.1 | <0.001<0.001<0.001<0.001<0.0010.0090.0570.5990.636<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, yearsaFemale, %Diabetes mellitus, %Chronic kidney diseases, %Oral corticosteroidb use, %Dose of oral corticosteroidsa, c, mg/dayFracture at baselined, % | 54.0 (44.0–61.0)89.911.55.723.95.0 (4.3–10.0)28.7 | 52.0 (42.0–60.0)75.63.91.96.55.0 (3.0–7.5)0.1 | <0.001<0.001<0.001<0.001<0.0010.019<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.