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Summary of Study Results Using National Database of Health Insurance Claims Japan (NDB)

March 2, 2026

Study title

Evaluation of the risk of fractures by pioglitazone hydrochloride

Products investigated

The following pioglitazone hydrochloride-containing preparations (hereinafter referred to as "pioglitazone"):

- Pioglitazone hydrochloride
- Alogliptin benzoate/pioglitazone hydrochloride combination products
- Pioglitazone hydrochloride/glimepiride combination products

Background:

- Previous studies, including clinical trials conducted outside of Japan, on pioglitazone showed a consistently increased risk of fractures in women, but not in men. Many of these previous studies were conducted in patients with type 2 diabetes mellitus in Europe and the United States, whereas studies in Asian countries, including Japan, are limited.
- In this study, the risk of fractures in patients with type 2 diabetes mellitus prescribed pioglitazone, including the differences by sex, was investigated using a large-scale medical information database in Japan.

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Purpose of the study

The purpose was to evaluate the fracture risk of pioglitazone in patients with type 2 diabetes mellitus in the overall study population and separately by sex, compared with that in those prescribed metformin hydrochloride-containing preparations.

Reason for selection of NDB for the study and data period

Reason for selection: It was selected because it is a nationwide database in Japan that enables follow-up of patients across different medical institutions.

Data period: August 1, 2010 to March 31, 2021

Outline of method

- **Study Design**

  Cohort design

- **Study population**

  Among patients who were prescribed or dispensed (hereinafter referred to as "prescribed") pioglitazone or metformin hydrochloride-containing preparations (hereinafter referred to as "metformin") [1] between April 1, 2012 and March 31, 2021, patients diagnosed with type 2 diabetes mellitus in the month of the earliest prescription date (t_0) or in the previous month were identified. Of these, patients meeting none of the exclusion criteria (1) to (4) were included in the study population. Patients prescribed pioglitazone at t_0 were classified into the exposure group and those prescribed metformin at t_0 were classified into the control group.

  (1) Patients who had no claim data for one year (12 months) or more before t_0

  (2) Patients who were prescribed both pioglitazone and metformin, or pioglitazone hydrochloride/metformin hydrochloride combination products, at t_0

  (3) Patients who had been prescribed pioglitazone, metformin, or pioglitazone hydrochloride/metformin hydrochloride combination products at any time before t_0

  (4) Patients whose t_0 was the end date of the month of the last claim data

[1] Metformin hydrochloride, anagliptin/metformin hydrochloride combination products, alogliptin benzoate/metformin hydrochloride combination products, or vildagliptin/metformin hydrochloride combination products

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■ **Follow-up period**

The start and end dates of the follow-up period were defined as follows:

- Start date of follow-up period: the day after t_0
- End date of follow-up period: the earliest date among the following:
  (1) End date of the prescription period [2]
  (2) Date of prescription of drugs classified into different groups (exposure group or control group)
  (3) Date of prescription of pioglitazone hydrochloride/metformin hydrochloride combination products
  (4) Date of outcome occurrence
  (5) End date of the month of the last claim data

[2] A prescription period was defined as a period during which prescriptions were considered to be continuous when the interval between the end date of the preceding prescription and the start date of the subsequent prescription was less than or equal to 63 days. The end date of the prescription period was defined as the end date of the last prescription plus 63 days (grace period).

■ **Outcomes**

- The outcome was defined as an examination (radiography) and procedures (surgical reduction or fixation of fractures, bone head or joint prosthesis replacement) performed within 14 days before and after the diagnosis date of fractures (the start date of treatment or the date of hospitalization). The diagnosis date of fractures was defined as the date of outcome occurrence.
- The outcomes defined were all fractures regardless of fracture site, and site-specific fractures (upper limb fractures, distal upper limb fractures, lower limb fractures, femur fractures, distal lower limb fractures, spinal fractures, rib and sternal fractures, pelvic fractures, and fractures at other sites).

■ **Analyses and methods**

- The primary analysis was performed using the Cox proportional hazards model to estimate the adjusted hazard ratios [3] and their 95% confidence intervals (CIs) for the occurrence of all fractures and site-specific fractures separately in the exposure group compared with the control group, in the overall study population and separately by sex.
- Subgroup analyses were performed using the same methods as the primary analysis, for all fractures in the following subgroups (1) to (4) among the overall study population:

(1) Patients by age group (<65 years, ≥65 years)
(2) Patients without a history of fractures
(3) Patients without prescriptions for other antidiabetic drugs[4]
(4) Patients without prescriptions for oral steroids

- Sensitivity analyses were performed for all fractures in the overall study population, with changes to the primary analysis, as shown in (1) to (3) below.
  (1) The diagnosis date of fractures was changed to the confirmed diagnosis date of fractures, and the procedures were excluded from the outcome definition.[5]
  (2) The time period was changed from 14 days to 7 days for the outcome definition.[6]
  (3) The grace period was changed to 365 days for the prescription period.

[3] Hazard ratios were adjusted for sex (only for evaluation of the overall study population), age, duration of type 2 diabetes mellitus, medical history (fractures, osteoporosis, rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease, and diabetic microangiopathy), and history of prescribed medications (dipeptidyl peptidase-4 inhibitors [DPP-4 inhibitors], sulfonylureas, sodium glucose cotransporter 2 inhibitors [SGLT2 inhibitors], insulin, oral steroids, and hypnotics).

[4] The study population was limited to patients who were not prescribed antidiabetic drugs other than pioglitazone or metformin (defined as other antidiabetics including DPP-4 inhibitors, sulfonylureas, SGLT2 inhibitors, rapid-acting insulin secretagogues, α-glycosidase inhibitors, glucagon-like peptide-1 receptor agonists, insulin, and combination products), and "the prescription date of other antidiabetics" was added as criterion (6) for the end date of the follow-up period.

[5] Outcome definition: Examination (radiography) was performed within 14 days before and after the confirmed diagnosis date of fractures.

[6] Outcome definition: Examination (radiography) and procedures (surgical reduction or fixation of fractures, bone head or joint prosthesis replacement) were performed within 7 days before and after the diagnosis date of fractures.

Outline of results

■ Study population

- The study population was 3,234,950 patients (397,080 in the exposure group; 2,837,870 in the control group), including 1,975,647 males (239,017 in the exposure group; 1,736,630 in the control group) and 1,259,303 females (158,063 in the exposure group; 1,101,240 in the control group) (Appendix Table 1-1 to Table 1-3).
- In the overall study population and in the male patient population, standardized differences exceeding 0.1 were observed between the exposure and control groups for the following factors: age, a history of chronic kidney disease and diabetic microangiopathy, and prescriptions for DPP-4 inhibitors, sulfonylureas, and SGLT2 inhibitors. In addition to these factors, the standardized difference for a history of osteoporosis exceeded 0.1 in the female patient population.

- **Adjusted hazard ratios of fractures in the exposure group compared with the control group**
  - In the primary analysis, the adjusted hazard ratios (95% CIs) for all fractures were 1.35 (1.33 - 1.37) in the overall study population, 1.30 (1.27 - 1.33) in the male patient population, and 1.38 (1.36 - 1.41) in the female patient population (Appendix Table 2).
  - In the primary analysis, the adjusted hazard ratios for site-specific fractures were particularly high at 1.61 (1.55 - 1.66) for distal lower limb fractures and at 1.48 (1.43 - 1.53) for distal upper limb fractures in the overall study population, and the lower limits of the CIs exceeded 1 for all site-specific fractures in the overall study population. In the male and female patient populations, the adjusted hazard ratios were also particularly high for distal lower limb fractures and distal upper limb fractures, and the lower limits of the CIs exceeded 1 for all site-specific fractures.
  - In all subgroup analyses, the adjusted hazard ratios ranged from 1.33 to 1.42, with the lower limits of the CIs exceeding 1 (Appendix Table 3).
  - In all sensitivity analyses, the adjusted hazard ratios ranged from 1.31 to 1.35, with the lower limits of the CIs exceeding 1 (Appendix Table 4).
- **Discussion based on the results**
  - The fracture risk of pioglitazone was higher than that of metformin in the overall study population, and similar findings were observed in all subgroup analyses and sensitivity analyses. Analyses for site-specific fractures showed that the risk of distal limb fractures was particularly high.
  - The evaluation conducted separately by sex also revealed that, in both males and females, the fracture risk of pioglitazone was higher than that of metformin, and there was no particular difference in the risk of fractures according to sex. Analyses for site-specific fractures also revealed no notable difference according to sex, indicating that the fracture risk of pioglitazone is similar in males and females.
  - It should be noted that there are some limitations in the interpretation of the results, including the following: Although the outcome definition of fractures was defined based on clinical perspectives, a validation study using the NDB has been unachievable; and the possibility that other potential confounders (e.g., bone mineral density, body mass index) may have affected the results cannot be ruled out.

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Appendix

Table 1-1. Patient Characteristics in the Exposure and Control Groups (Overall Study Population)

	Exposure group (N = 397,080)		Control group (N = 2,837,870)	
	N	(%)	N	(%)
Sex				
Male	239,017	(60.19)	1,736,630	(61.19)
Female	158,063	(39.81)	1,101,240	(38.81)
Age				
≤ 29 years	3,199	(0.81)	47,332	(1.67)
30 to 39 years	11,709	(2.95)	142,429	(5.02)
40 to 49 years	35,590	(8.96)	384,656	(13.55)
50 to 59 years	62,934	(15.85)	578,633	(20.39)
60 to 64 years	49,953	(12.58)	374,994	(13.21)
65 to 69 years	57,918	(14.59)	442,243	(15.58)
70 to 74 years	57,425	(14.46)	364,033	(12.83)
75 to 79 years	52,358	(13.19)	254,428	(8.97)
80 to 84 years	38,976	(9.82)	151,221	(5.33)
85 to 89 years	19,713	(4.96)	71,179	(2.51)
≥ 90 years	7,305	(1.84)	26,722	(0.94)
Duration of type 2 diabetes mellitus				
< 3 years	128,326	(32.32)	946,730	(33.36)
≥ 3 to < 5 years	67,218	(16.93)	430,853	(15.18)
≥ 5 to < 7 years	57,568	(14.50)	427,761	(15.07)
≥ 7 to < 9 years	45,391	(11.43)	372,826	(13.14)
≥ 9 to < 10 years	17,966	(4.52)	145,903	(5.14)
≥ 10 years	80,611	(20.30)	513,797	(18.11)
History of disease				
Fractures	32,495	(8.18)	245,881	(8.66)
Osteoporosis	32,916	(8.29)	170,886	(6.02)
Rheumatoid arthritis	40,991	(10.32)	318,318	(11.22)
Chronic kidney disease	111,493	(28.08)	985,296	(34.72)
Chronic obstructive pulmonary disease	11,034	(2.78)	84,318	(2.97)
Diabetic microangiopathy	160,067	(40.31)	1,356,432	(47.80)
History of prescribed or dispensed medications				
DPP-4 inhibitors	268,571	(67.64)	1,702,234	(59.98)
Sulfonylureas	133,896	(33.72)	598,431	(21.09)
SGLT2 inhibitors	18,168	(4.58)	243,906	(8.59)
Insulin	43,383	(10.93)	392,873	(13.84)
Oral steroids	20,021	(5.04)	138,781	(4.89)
Hypnotics	73,558	(18.52)	429,319	(15.13)

Abbreviation: DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT2 inhibitors, sodium glucose cotransporter 2 inhibitors

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Table 1-2. Patient Characteristics in the Exposure and Control Groups (Male Patient Population)

	Exposure group (n = 239,017)		Control group (n = 1,736,630)	
	N	(%)	N	(%)
Age				
≤ 29 years	2,022	(0.85)	26,238	(1.51)
30 to 39 years	8,245	(3.45)	91,896	(5.29)
40 to 49 years	26,772	(11.20)	275,891	(15.89)
50 to 59 years	43,183	(18.07)	385,195	(22.18)
60 to 64 years	31,988	(13.38)	235,098	(13.54)
65 to 69 years	35,432	(14.82)	265,633	(15.30)
70 to 74 years	33,028	(13.82)	207,681	(11.96)
75 to 79 years	28,595	(11.96)	137,610	(7.92)
80 to 84 years	19,475	(8.15)	74,374	(4.28)
85 to 89 years	8,130	(3.40)	29,347	(1.69)
≥ 90 years	2,147	(0.90)	7,667	(0.44)
Duration of type 2 diabetes mellitus				
< 3 years	81,606	(34.14)	602,299	(34.68)
≥ 3 to < 5 years	41,694	(17.44)	270,969	(15.60)
≥ 5 to < 7 years	34,669	(14.50)	263,891	(15.20)
≥ 7 to < 9 years	26,672	(11.16)	225,507	(12.99)
≥ 9 to < 10 years	10,397	(4.35)	86,337	(4.97)
≥ 10 years	43,979	(18.40)	287,627	(16.56)
History of disease				
Fractures	13,601	(5.69)	114,283	(6.58)
Osteoporosis	5,149	(2.15)	28,488	(1.64)
Rheumatoid arthritis	18,083	(7.57)	143,738	(8.28)
Chronic kidney disease	68,911	(28.83)	620,187	(35.71)
Chronic obstructive pulmonary disease	8,532	(3.57)	64,161	(3.69)
Diabetic microangiopathy	96,286	(40.28)	839,064	(48.32)
History of prescribed or dispensed medications				
DPP-4 inhibitors	163,036	(68.21)	1,048,190	(60.36)
Sulfonylureas	80,710	(33.77)	368,145	(21.20)
SGLT2 inhibitors	11,777	(4.93)	158,466	(9.12)
Insulin	25,625	(10.72)	244,104	(14.06)
Oral steroids	10,690	(4.47)	73,255	(4.22)
Hypnotics	35,113	(14.69)	210,122	(12.10)

Abbreviation: DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT2 inhibitors, sodium glucose cotransporter 2 inhibitors

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Table 1-3. Patient Characteristics in the Exposure and Control Groups (Female Patient Population)

	Exposure group (N = 158,063)		Control group (N = 1,101,240)	
	N	(%)	N	(%)
Age				
≤ 29 years	1,177	(0.74)	21,094	(1.92)
30 to 39 years	3,464	(2.19)	50,533	(4.59)
40 to 49 years	8,818	(5.58)	108,765	(9.88)
50 to 59 years	19,751	(12.50)	193,438	(17.57)
60 to 64 years	17,965	(11.37)	139,896	(12.70)
65 to 69 years	22,486	(14.23)	176,610	(16.04)
70 to 74 years	24,397	(15.43)	156,352	(14.20)
75 to 79 years	23,763	(15.03)	116,818	(10.61)
80 to 84 years	19,501	(12.34)	76,847	(6.98)
85 to 89 years	11,583	(7.33)	41,832	(3.80)
≥ 90 years	5,158	(3.26)	19,055	(1.73)
Duration of type 2 diabetes mellitus				
< 3 years	46,720	(29.56)	344,431	(31.28)
≥ 3 to < 5 years	25,524	(16.15)	159,884	(14.52)
≥ 5 to < 7 years	22,899	(14.49)	163,870	(14.88)
≥ 7 to < 9 years	18,719	(11.84)	147,319	(13.38)
≥ 9 to < 10 years	7,569	(4.79)	59,566	(5.41)
≥ 10 years	36,632	(23.18)	226,170	(20.54)
History of disease				
Fractures	18,894	(11.95)	131,598	(11.95)
Osteoporosis	27,767	(17.57)	142,398	(12.93)
Rheumatoid arthritis	22,908	(14.49)	174,580	(15.85)
Chronic kidney disease	42,582	(26.94)	365,109	(33.15)
Chronic obstructive pulmonary disease	2,502	(1.58)	20,157	(1.83)
Diabetic microangiopathy	63,781	(40.35)	517,368	(46.98)
History of prescribed or dispensed medications				
DPP-4 inhibitors	105,535	(66.77)	654,044	(59.39)
Sulfonylureas	53,186	(33.65)	230,286	(20.91)
SGLT2 inhibitors	6,391	(4.04)	85,440	(7.76)
Insulin	17,758	(11.23)	148,769	(13.51)
Oral steroids	9,331	(5.90)	65,526	(5.95)
Hypnotics	38,445	(24.32)	219,197	(19.90)

Abbreviation: DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT2 inhibitors, sodium glucose cotransporter 2 inhibitors

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Table 2. Adjusted Hazard Ratios and Their 95% CIs for the Fractures (Primary Analysis)

	Exposure group			Control group			Adjusted hazard ratio [1]	
	Number of outcomes	Total follow-up period (1,000 person-years)	Incidence rate (/1,000 person-years)	Number of outcomes	Total follow-up period (1,000 person-years)	Incidence rate (/1,000 person-years)	Estimate	(95% CI)
Overall study population								
All fractures	22,761	804.93	28.28	114,823	6,347.18	18.09	1.35	(1.33-1.37)
Upper limb fracture	6,145	835.44	7.36	30,205	6,510.17	4.64	1.42	(1.38-1.46)
Distal upper limb fracture	4,634	838.06	5.53	22,301	6,524.15	3.42	1.48	(1.43-1.53)
Lower limb fracture	7,352	835.73	8.80	33,713	6,512.49	5.18	1.44	(1.40-1.48)
Femur fracture	3,346	843.76	3.97	13,760	6,553.98	2.10	1.26	(1.21-1.31)
Distal lower limb fracture	4,264	839.02	5.08	20,826	6,527.35	3.19	1.61	(1.55-1.66)
Spinal fracture	4,829	839.38	5.75	20,980	6,534.82	3.21	1.34	(1.30-1.39)
Rib and sternal fractures	5,099	837.60	6.09	30,255	6,510.23	4.65	1.14	(1.10-1.17)
Pelvic fracture	640	846.49	0.76	3,065	6,565.11	0.47	1.29	(1.18-1.40)
Fractures at other sites	5,825	835.57	6.97	27,422	6,511.79	4.21	1.47	(1.43-1.51)
Male								
All fractures	9,193	504.01	18.24	48,341	3,883.52	12.45	1.30	(1.27-1.33)
Upper limb fracture	2,135	517.01	4.13	11,371	3,954.72	2.88	1.34	(1.28-1.40)
Distal upper limb fracture	1,500	518.05	2.90	7,982	3,960.83	2.02	1.36	(1.29-1.44)
Lower limb fracture	2,574	516.87	4.98	12,083	3,955.40	3.05	1.44	(1.38-1.51)
Femur fracture	936	520.13	1.80	3,770	3,972.34	0.95	1.31	(1.22-1.41)
Distal lower limb fracture	1,706	517.73	3.30	8,555	3,959.40	2.16	1.52	(1.44-1.60)
Spinal fracture	1,743	518.33	3.36	7,645	3,964.36	1.93	1.31	(1.24-1.38)
Rib and sternal fractures	2,658	516.01	5.15	15,822	3,945.75	4.01	1.14	(1.10-1.19)
Pelvic fracture	254	520.70	0.49	1,285	3,974.63	0.32	1.28	(1.11-1.46)
Fractures at other sites	2,332	516.47	4.52	11,596	3,952.13	2.93	1.41	(1.34-1.47)
Female								
All fractures	13,568	300.92	45.09	66,482	2,463.66	26.99	1.38	(1.36-1.41)
Upper limb fracture	4,010	318.43	12.59	18,834	2,555.44	7.37	1.47	(1.42-1.52)
Distal upper limb fracture	3,134	320.00	9.79	14,319	2,563.32	5.59	1.54	(1.48-1.60)
Lower limb fracture	4,778	318.86	14.98	21,630	2,557.09	8.46	1.43	(1.39-1.48)
Femur fracture	2,410	323.63	7.45	9,990	2,581.64	3.87	1.24	(1.18-1.30)
Distal lower limb fracture	2,558	321.28	7.96	12,271	2,567.95	4.78	1.67	(1.60-1.74)
Spinal fracture	3,086	321.05	9.61	13,335	2,570.46	5.19	1.36	(1.31-1.42)
Rib and sternal fractures	2,441	321.59	7.59	14,433	2,564.48	5.63	1.13	(1.08-1.18)
Pelvic fracture	386	325.79	1.18	1,780	2,590.48	0.69	1.29	(1.16-1.45)
Fractures at other sites	3,493	319.11	10.95	15,826	2,559.66	6.18	1.51	(1.46-1.57)

[1] Hazard ratios were estimated using the Cox proportional hazards model and adjusted for sex (only for evaluation of the overall study population), age, duration of type 2 diabetes mellitus, medical history (fractures, osteoporosis, rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease, and diabetic microangiopathy), and history of prescribed medications (dipeptidyl peptidase-4 inhibitors, sulfonylureas, sodium glucose cotransporter 2 inhibitors, insulin, oral steroids, and hypnotics).

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Table 3. Adjusted Hazard Ratios and Their 95% CIs for the Fractures (Subgroup Analyses)

	Exposure group			Control group			Adjusted hazard ratio [1]	
	Number of outcomes	Total follow-up period (1,000 person-years)	Incidence rate (/1,000 person-years)	Number of outcomes	Total follow-up period (1,000 person-years)	Incidence rate (/1,000 person-years)	Estimate	(95% CI)
Age groups								
Patients < 65 years of age	5,451	341.63	15.96	40,967	3,555.42	11.52	1.40	(1.36-1.44)
Patients ≥ 65 years of age	17,310	463.30	37.36	73,856	2,791.76	26.45	1.33	(1.30-1.35)
Patients without a history of fractures	19,366	757.39	25.57	94,619	5,935.43	15.94	1.36	(1.34-1.39)
Patients without prescriptions for other antidiabetics [2]	2,735	113.96	24.00	13,276	919.89	14.43	1.42	(1.36-1.48)
Patients without prescriptions for oral steroids	21,525	774.33	27.80	107,656	6,097.15	17.66	1.35	(1.33-1.37)

[1] Hazard ratios were estimated using the Cox proportional hazards model and adjusted for sex, age, duration of type 2 diabetes mellitus, medical history (fractures, osteoporosis, rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease, and diabetic microangiopathy), and history of prescribed medications (dipeptidyl peptidase-4 inhibitors, sulfonylureas, sodium glucose cotransporter 2 inhibitors, insulin, oral steroids, and hypnotics).

[2] The study population was limited to patients who were not prescribed antidiabetic drugs other than pioglitazone hydrochloride-containing preparations or metformin hydrochloride-containing preparations (defined as other antidiabetics including dipeptidyl peptidase-4 inhibitors, sulfonylureas, sodium glucose cotransporter 2 inhibitors, rapid-acting insulin secretagogues, α-glycosidase inhibitors, glucagon-like peptide-1 receptor agonists, insulin, and combination products), and “the start date of other antidiabetics” was added as criterion (6) for the end date of the follow-up.

Table 4. Adjusted Hazard Ratios and Their 95% CIs for the Fractures (Sensitivity Analyses)

	Exposure group			Control group			Adjusted hazard ratio [1]	
	Number of outcomes	Total follow-up period (1,000 person-years)	Incidence rate (/1,000 person-years)	Number of outcomes	Total follow-up period (1,000 person-years)	Incidence rate (/1,000 person-years)	Estimate	(95% CI)
Modified outcome definition 1 [2]	36,500	781.05	46.73	189,979	6,209.49	30.59	1.31	(1.29-1.32)
Modified outcome definition 2 [3]	21,887	806.20	27.15	110,536	6,354.12	17.40	1.35	(1.33-1.37)
Modified grace period [4]	27,511	957.01	28.75	134,496	7,221.06	18.63	1.32	(1.30-1.33)

[1] Hazard ratios were estimated using the Cox proportional hazards model and adjusted for sex, age, duration of type 2 diabetes mellitus, medical history (fractures, osteoporosis, rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease, and diabetic microangiopathy), and history of prescribed medications (dipeptidyl peptidase-4 inhibitors, sulfonylureas, sodium glucose cotransporter 2 inhibitors, insulin, oral steroids, and hypnotics).

[2] Outcome definition: Examination (radiography) was performed within 14 days before and after the confirmed diagnosis date of fractures.

[3] Outcome definition: Examination (radiography) and procedures (surgical reduction or fixation of fractures, bone head or joint prosthesis replacement) were performed within 7 days before and after the diagnosis date of fractures.

[4] Grace period: 365 days

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