Clinical Research Article

Effect of a Multifactorial Intervention on Fracture in Patients With Type 2 Diabetes: Subanalysis of the J-DOIT3 Study

Takayoshi Sasako,1 Kohjiro Ueki,2 Kana Miyake,1 Yukiko Okazaki,1,3 Yasuhiro Takeuchi,4,5 Yasuo Ohashi,6 Mitsuhiko Noda,7,8 and Takashi Kadowaki1,9,10

1Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan; 2Department of Molecular Diabetic Medicine, Diabetes Research Center, National Center for Global Health and Medicine, Tokyo 162-8655, Japan; 3Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine, Tokyo 177-8521, Japan; 4Toranomon Hospital Endocrine Center, Tokyo 105-8470, Japan; 5Okinaka Memorial Institute for Medical Research, Tokyo 105-8470, Japan; 6Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo 112-8551, Japan; 7Ichikawa Hospital, International University of Health and Welfare, Ichikawa 272-0827, Japan; 8Department of Endocrinology and Diabetes, Saitama Medical University, Saitama 350-0495, Japan; 9Department of Prevention of Diabetes and Lifestyle-Related Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan; and 10Toranomon Hospital, Tokyo 105-8470, Japan

ORCID numbers: 0000-0002-7644-309X (T. Sasako); 0000-0002-5428-3582 (T. Kadowaki).

Abbreviations: BMD, bone mineral density; HbA1c, glycated hemoglobin A1c; LDL, low-density lipoprotein; TZD, thiazolidinedione.

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Abstract

Aims: To evaluate the effects of an intensified multifactorial intervention and patient characteristics on the incidence of fractures comorbid with type 2 diabetes.

Methods: Fracture events were identified and analyzed among adverse events reported in the J-DOIT3 study, a multicenter, open-label, randomized, parallel-group trial that was conducted in Japan, in which patients with type 2 diabetes were randomly assigned to receive conventional therapy for glucose, blood pressure, and lipids (targets: HbA1c < 6.9%, blood pressure <130/80 mm Hg, LDL-cholesterol <120mg/dL) or intensive therapy (HbA1c < 6.2%, blood pressure <120/75 mm Hg, LDL-cholesterol <80mg/dL) (ClinicalTrials.gov registration no. NCT00300976).

Results: The cumulative incidence of fractures did not differ between those receiving conventional therapy and those receiving intensive therapy (hazard ratio (HR) 1.15; 95% CI, 0.91-1.47; P = 0.241). Among the potential risk factors, only history of smoking at baseline was significantly associated with the incidence of fractures in men (HR 1.96; 95% CI, 1.04-3.07; P = 0.038). In contrast, the incidence of fractures in women was associated...
Growing attention has been focused for the past 2 decades on bone fracture as a novel comorbidity of diabetes. Fracture risk is shown to be elevated in patients with diabetes and it has been attributed to impaired bone quality through various mechanisms (1-3). It is noteworthy that patients with type 2 diabetes have relatively higher bone mineral density (BMD) but are more prone to fracture than those without (1-3), given that BMD is thought to be closely associated with fracture risk.

Although the FRAX score, available through a web-based risk engine (4), is currently widely used to predict the 10-year probability of developing fractures, fracture prediction based on this score was reported to underestimate the incidence of fractures in patients with type 2 diabetes (5, 6).

Moreover, the fracture risk is shown to be affected by treatment of diabetes. Classically, it is known to be elevated by poor glycemic control, hypoglycemia, and, among antidiabetic drugs, thiazolidinediones (TZDs) (1-3, 7, 8). TZDs are shown to affect mesenchymal stem cells, the common precursors of adipocytes and osteoblasts, promoting their differentiation into the former and thus resulting in a decrease in the latter, possibly via activation of peroxisome proliferator-activated receptor γ (9-11). Thus, TZDs impair bone formation and deteriorate the mechanical properties of bone.

In several clinical trials, the incidence of fractures reported as adverse events were increased in patients receiving rosiglitazone or pioglitazone, mainly in women with type 2 diabetes (12-16). It was also increased in those receiving insulin or a sodium–glucose co-transporter-2 (SGLT2) inhibitor (17, 18), those with major hypoglycemic episodes, or those with poor adherence with study drug (14), and it was decreased in those receiving metformin (17). The incidence of fractures was not affected by intensive glucose control (19), intensive blood pressure control (20), or intensive lifestyle modification (21), but to date, no study was found to examine the effects of intensive multifactorial intervention on fractures. Although some baseline risk factors were identified, including female sex, long duration of diabetes, and older age (14), as well as chronic kidney disease (22), no subanalysis has been performed to examine both the quantified fracture risk at baseline and effects of intervention on the subsequent incidence of fractures.

In Japan, although the fracture risk was reported to be elevated in both men and women with type 2 diabetes (23), it remained unclear whether the FRAX score could serve as a good predictor of fractures in patients with type 2 diabetes. In a prospective randomized trial undertaken in Japan, administration of pioglitazone was not associated with an increased risk of fractures, although the analysis was performed irrespective of sex (24).

Recently, we reported the primary results of the J-DOIT3 (Japan Diabetes Optimal Treatment study for 3 major risk factors of cardiovascular diseases), a randomized trial undertaken in Japan in which 2,540 patients with type 2 diabetes were followed for a median of 8.5 years (25-27). Major risk factors for cardiovascular diseases were significantly better in the intensive therapy group during the intervention period, including glycated hemoglobin (HbA1c) (6.8% [51.0 mmol/mol] in the intensive therapy group vs 7.2% [55.2 mmol/mol] in the conventional therapy group, respectively on average). Body mass index during the intervention period (24.8 vs 24.7) was almost identical to that at baseline in both groups (24.8 vs 24.9). The intensive therapy was associated with a nonsignificant risk reduction in the primary outcome composed of myocardial infarction, stroke, revascularization, and all-cause mortality (hazard ratio [HR] 0.81), and in a post hoc breakdown, it was associated with a significant risk reduction in cerebrovascular events composed of stroke and cerebrovascular revascularization (HR 0.42) (27). It was also associated with a significant risk reduction in renal events (HR 0.68) (27, 28). To achieve tight glycemic control without causing severe hypoglycemia, pioglitazone was more frequently used in the intensive therapy group (42% vs 24%, at the final visit), and indeed, the incidence of severe hypoglycemia was quite low in both groups (0.6% vs 0.3%) during the intervention period. Still, the incidence of any hypoglycemia was higher in the intensive therapy group (41% vs 22%), presumably in association with improved glycemic control (27).

with the FRAX score [%/10 years] at baseline (HR 1.04; 95% CI, 1.02-1.07; P < 0.001) and administration of pioglitazone at 1 year after randomization (HR 1.59; 95% CI, 1.06-2.38; P = 0.025).

Conclusions: Intensified multifactorial intervention may be implemented without increasing the fracture risk in patients with type 2 diabetes. The fracture risk is elevated in those with a history of smoking in men, whereas it is predicted by the FRAX score and is independently elevated with administration of pioglitazone in women.

Key Words: clinical trial, type 2 diabetes, osteoporosis, fracture risk assessment, therapeutics, epidemiology
Among other prespecified adverse events, patients in whom at least an event of fracture was reported were slightly increased in the intensive therapy group compared with the conventional therapy group (143 [11%] vs 125 [10%]) (27). Although this increase was not statistically significant, it prompted us to examine the effects of intensive therapy on bone health. We also explored how patients with type 2 diabetes at high risk of fractures may be identified by drawing on the large-scale and long-term dataset obtained during the intervention period in the J-DOIT3 study.

Methods and Materials

Study Outline

This multicenter open-label, randomized, parallel-group trial examined the efficacy of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes. A detailed outline of the trial was described previously (26, 27), but in brief, a total of 2542 patients with type 2 diabetes, with hypertension and/or dyslipidemia, were registered at 81 clinical sites in Japan. The patients were randomly assigned at a 1:1 ratio to either conventional therapy for treatment targets of HbA1c, blood pressure, and lipids (HbA1c <6.9%, blood pressure <130/80 mm Hg, and low-density lipoprotein (LDL) cholesterol <120mg/dL), specified in the Japanese guideline (29), or intensive therapy for stricter treatment targets (HbA1c <6.2%, blood pressure <120/75 mm Hg, LDL-cholesterol <80 mg/dL).

Two patients were found ineligible after randomization and excluded from all the analyses, leaving a total of 2540 patients for the intention-to-treat population.

The primary outcome for the study was occurrence of any of a composite of myocardial infarction, stroke, revascularization (coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting), and all-cause mortality (26). Patients with the FRAX score no less than 15%/10 years were deemed to be at high risk of fractures according to the Japanese guideline (31).

Assessment of the FRAX Score

At the end of the intervention period, the physicians in charge were asked to assess the FRAX score (for prediction of major osteoporotic fractures) without BMD of each patient at registration retrospectively, by entering relevant risk factors (age, sex, body weight, height, prior history of fracture, history of parental hip fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and alcohol intake) in the web-based risk engine (4). The data were collected through the electronic data capturing system (26). Patients with the FRAX score no less than 15%/10 years were deemed to be at high risk of fractures according to the Japanese guideline (31).

Statistical Considerations

Cumulative incidence of fractures was estimated by the Kaplan-Meier method, and incidence rates were estimated by the nonparametric person-years method with appropriate stratification.

The hazard ratios for potential background risk factors were estimated by the Cox regression, as in the analysis of the primary outcome (27), and the backward elimination procedure was applied for selecting influential risk factors with the threshold of $P = 0.10$.

The landmark analysis using the data 1 year after randomization was applied for evaluating the effect of pioglitazone for fractures, which was administered in only 192 out of 2540 patients (7.6%) at baseline (27), but in 940 patients (37.0%) at 1 year, which was greater than 829 patients (32.6%) at the last visit (27). Any hypoglycemia reported as an adverse event before the first fracture event
was included in the explanatory covariates, and hypotension, defined as systolic blood pressure less than 100 mmHg at any visit before the first fracture event, was included as well, instead of any instances of hypotension reported as an adverse event, which were very few (<10).

Statistical significance was judged when two-sided \( P < 0.05 \). For declaring a binary risk factor (evenly distributed in 0 and 1) with the true hazard ratio of 1.50, 1.75, and 2.00 as statistically significant, the necessary number of events for power >0.90 were estimated as 256, 135, and 88, respectively. Observed number of fractures (all: 268; with FRAX score at baseline: 217) was judged enough for detecting and discussing the clinical significance of risk factors with hazard ratio >1.50-1.75. Any missing values were not imputed. All analyses were conducted using SAS version 9.4.

**Results**

**Effects of Intensive Therapy on the Incidence of Fractures**

During the intervention period of the J-DOIT3 study, adverse events, including fracture events, were followed for a mean of 7.8 years (SD 1.9). The incidence of fractures during the intervention period was 0.013 per person-year (95% CI, 0.011-0.016) in the conventional therapy group and 0.015 per person-year (95% CI, 0.013-0.018) in the intensive therapy group (Table 1).

An examination of the cumulative incidence of fractures showed that intensive therapy was not associated with an increased incidence of fractures compared with conventional therapy during the intervention period (HR 1.15; 95% CI, 0.91-1.47; \( P = 0.241 \); Fig. 1A). Given that osteoporosis and fracture differ in incidence between men and women, we conducted a sex-stratified analysis and found that, compared with the incidence of fractures in men in the conventional therapy group, the incidence in men in the intensive therapy group was not elevated (HR 1.18; 95% CI, 0.83-1.69), and the incidence of fractures in women in the conventional therapy group (HR 2.12; 95% CI, 1.49-3.01) was similar to that in women in the intensive therapy group (HR 2.37; 95% CI, 1.68-3.34). The incidence was significantly associated with sex \( (P < 0.001) \), but not with therapy group \( (P = 0.252) \) or the interaction \( (P = 0.821) \) (Fig. 1B).

We further performed Cox regression analysis using the prespecified baseline risk factors and found that intensive therapy was not associated with an increased fracture risk even after adjustment (HR 1.13; 95% CI,

**Table 1. Annual Incidence of Fractures**

| Year | No. at risk | No. of patients \( ^a \) | Person-years at risk | Incidence per person-year |
|------|-------------|--------------------------|---------------------|---------------------------|
| 0-1  | 1271        | 10                       | 1253.3              | 0.008                     |
| 1-2  | 1237        | 18                       | 1218.7              | 0.015                     |
| 2-3  | 1203        | 13                       | 1186.4              | 0.011                     |
| 3-4  | 1170        | 9                        | 1150.5              | 0.008                     |
| 4-5  | 1134        | 15                       | 1113.0              | 0.013                     |
| 5-6  | 1095        | 22                       | 1073.5              | 0.020                     |
| 6-7  | 1056        | 12                       | 1039.5              | 0.012                     |
| 7-8  | 1016        | 9                        | 825.6               | 0.011                     |
| 8-9  | 684         | 16                       | 522.1               | 0.031                     |
| 9-10 | 267         | 1                        | 67.0                | 0.015                     |

**Intensive therapy group (143 patients)**

| Year | No. at risk | No. of patients \( ^a \) | Person-years at risk | Incidence per person-year |
|------|-------------|--------------------------|---------------------|---------------------------|
| 0-1  | 1269        | 21                       | 1239.3              | 0.017                     |
| 1-2  | 1218        | 10                       | 1206.3              | 0.008                     |
| 2-3  | 1193        | 21                       | 1169.7              | 0.018                     |
| 3-4  | 1155        | 15                       | 1138.7              | 0.013                     |
| 4-5  | 1125        | 18                       | 1104.9              | 0.016                     |
| 5-6  | 1090        | 18                       | 1075.9              | 0.017                     |
| 6-7  | 1060        | 20                       | 1039.4              | 0.019                     |
| 7-8  | 1007        | 15                       | 814.1               | 0.018                     |
| 8-9  | 670         | 5                        | 510.4               | 0.010                     |
| 9-10 | 265         | 0                        | 70.2                | 0.000                     |

\( ^a \) The number of patients with their first fracture event reported.
0.88-1.44; \( P = 0.334 \) (Table 2). Indeed, among the explanatory covariates evaluated, sex showed the highest HR (HR 2.49; 95% CI, 1.82-3.39; \( P < 0.001 \)), followed by history of smoking (HR 1.46; 95% CI, 1.07-1.99; \( P = 0.017 \)) and duration of diabetes (HR 1.33; 95% CI, 1.03-1.70; \( P = 0.028 \)) (Table 2). Given the clear sex difference in fracture confirmed in this population, the following analyses were performed separately in men and women. The mean follow-up period in men was 7.8 years (SD 1.9), almost equivalent to that in women, which was 7.9 years (SD 1.8).

### Exploration of Fracture Risk Predictors at Baseline

Next, we explored fracture risk predictors in patients with type 2 diabetes in detail. FRAX score (major osteoporotic) without BMD was evaluated in a total of 1043 patients out of the 1575 men in both therapy groups (66.2%) and a total of 670 patients out of the 965 women in both therapy groups (69.4%). The FRAX score and the proportion of patients with the FRAX score no less than 15%/10 years were higher in women than in men, but similar between the therapy groups (Table 3 and Fig. 2). No difference was seen in the baseline characteristics between patients who had had their FRAX score evaluated and those who had not, except triglycerides, which were slightly lower with statistical significance in men and women who had their FRAX scores evaluated (data not shown).

Then we examined the cumulative incidence of fractures stratified by the baseline FRAX score. It was higher in women with FRAX score < 15%/10 years than in men with FRAX score < 15%/10 years (HR 1.45; 95% CI, 1.05-1.99), and was still higher in women with FRAX score ≥15%/10 years (HR 2.70; 95% CI, 1.93-3.76), although it was lower in men with FRAX score ≥15%/10 years (HR 0.34; 95% CI, 0.13-0.93; only 4 events in 114 patients). The incidence was not associated with the FRAX score (\( P = 0.403 \)) but was significantly associated with sex (\( P < 0.001 \)) and the interaction (\( P = 0.002 \) (Fig. 1C). Moreover, we examined the interaction between the potential risk factors at baseline by Cox regression analysis (data not shown) and found that the interaction was only significant between sex and the FRAX score, thus providing the rationale for analyses using the sex-stratified FRAX score.
Effects of Treatment Regimen and Related Adverse Events on the Incidence of Fractures

We further examined whether the baseline fracture risk might be modified by the intervention treatment by Cox regression analysis, or the landmark analysis, with 31 patients (15 in men and 16 in women) with the first fracture event during the intervention period within 1 year after randomization excluded.

In men, the only explanatory covariate shown to be significantly associated with the incidence of fractures was history of smoking at baseline (HR 1.96; 95% CI, 1.04-3.07; \( P = 0.038 \)) (Table 4). The baseline FRAX score was not associated with the incidence of fractures in men (Table 4), consistently with the analysis stratified by the FRAX score stated above (Fig. 1C).

In contrast, in women, the incidence of fractures was associated with the baseline FRAX score (HR 1.04; 95% CI, 1.02-1.07; \( P < 0.001 \)) and administration of pioglitazone at 1 year (HR 1.59; 95% CI, 1.06-2.38; \( P = 0.025 \)). The incidence of fractures was also positively, albeit not significantly, associated with history of smoking at baseline (HR 1.51; 95% CI, 0.93-2.45; \( P = 0.096 \)) (Table 4).

Again, therapy group and glycemic control were not associated with the incidence of fractures in either sex, whereas the duration of diabetes was not in the Cox regression analysis performed separately in both sexes. Moreover, neither hypoglycemia nor hypotension was associated with the incidence of fractures. There was no report of fractures associated with hypoglycemia or
hypotension, except a spine fracture due to hypotension after hemodialysis in a man in the conventional therapy group. Another woman in the conventional therapy group had a fibula fracture associated with a fall due to nighttime dizziness, but its association with hypoglycemia or hypotension was not clear.

Table 4. Cox regression Analysis of Fractures With Potential Risk Factors at Baseline and During the Intervention Period as Covariates

| Men                        | Hazard ratio | 95% CI       | P Value |
|----------------------------|--------------|--------------|---------|
| Therapy group              |              |              |         |
| Conventional / Intensive   | 1.123        | 0.708 - 1.784 | 0.622   |
| FRAX at baseline [%/10 years] | 0.988        | 0.952 - 1.026 | 0.541   |
| History of smoking at baseline | 1.962        | 1.040 - 3.701 | 0.038   |
| Duration of diabetes at baseline | 1.247        | 0.808 - 1.923 | 0.318   |
| Administration of pioglitazone at 1 year | 1.129        | 0.716 - 1.782 | 0.602   |
| Any hypoglycemic episode a | No / Yes     | 0.898        | 0.562 - 1.435 | 0.654   |
| Hypotension (systolic blood pressure <100 mmHg) at any visit a | No / Yes     | 0.571        | 0.248 - 1.314 | 0.188   |

| Women                      | Hazard ratio | 95% CI       | P Value |
|----------------------------|--------------|--------------|---------|
| Therapy group              |              |              |         |
| Conventional / Intensive   | 0.977        | 0.644 - 1.482 | 0.913   |
| FRAX at baseline [%/10 years] | 1.044        | 1.022 - 1.067 | <0.001  |
| History of smoking at baseline | 1.508        | 0.929 - 2.447 | 0.096   |
| Duration of diabetes at baseline | 1.158        | 0.770 - 1.741 | 0.482   |
| Administration of pioglitazone at 1 year | 1.589       | 1.061 - 2.380 | 0.025   |
| Any hypoglycemic episode a | No / Yes     | 0.891        | 0.592 - 1.341 | 0.580   |
| Hypotension (systolic blood pressure <100 mmHg) at any visit a | No / Yes     | 0.604        | 0.303 - 1.203 | 0.151   |

Cox regression analysis of fracture events 1 year after randomization was performed with potential prognostic factors at baseline and those during the intervention period as covariates. The patients were excluded in whom (1) the FRAX score at baseline was missing, (2) the duration of diabetes at baseline was missing, or (3) an event of fracture was reported within the first year after randomization, and 1011 men and 648 women were subjected to the analysis, respectively. HR to the control category shown left to the slash, or per 1 unit. a Before either the incidence of fracture (in patients who had fracture(s)) or the end of the intervention period (in those who did not).
Among the first fracture events whose situation of frac-ture was reported, we identified those associated with falls (eg, falls on the ground and those from stairs). In women, 31 out of 42 events (73.8%) in the conventional therapy group and 31 out of 44 events (70.5%) in the intensive therapy group were associated with falls, whereas in men, 21 out of 34 events (61.8%) in the conventional therapy group and 28 out of 42 events (66.7%) in the intensive therapy group were associated with falls. In both sexes, a statistically significant increase in fracture events associated with falls was not observed in the intensive therapy group by Fisher’s exact test.

Risk Predictors and Fracture Sites
Lastly, we focused on the incidence of major osteoporotic fractures. Among 268 patients who developed fracture(s), the first fracture event was thought likely to be a major osteoporotic fracture in 24 out of 121 men (19.8%) and 44 out of 147 women (29.9%) (Table 5). We explored the FRAX score threshold for major osteoporotic fractures in women, by Cox regression analysis with categorized FRAX scores. The incidence of major osteoporotic fractures was shown to be nearly proportional to the FRAX score with no clear threshold, but the incidence of fractures at other sites was significantly higher in women with baseline FRAX score >20%/10 years than in those with baseline FRAX score < 10%/10 years (Table 6). The administration of pioglitazone was associated with a statistically nonsignificant increase in the incidence of major osteoporotic fractures but was not associated with the incidence of fractures at other sites (Table 6).

### Discussion
In the management of diabetes, it is vitally important to implement appropriate measures against not only diabetic comorbidities but also treatment-associated adverse events. The J-DOIT3 study has shown that the intensified multifactorial intervention decreased diabetic comorbidities in patients with type 2 diabetes, with very low incidences of severe hypoglycemia and heart failure (27). The present study further adds evidence for the safety of intensive therapy, in that it is not associated with an increased risk of fractures.

It is one of our strengths that the FRAX score (major osteoporotic) without BMD at registration was assessed to predict the risk of fractures within 10 years (4), enabling us to examine both the quantified baseline fracture risk and the effects of intervention treatment of the J-DOIT3 study on the incidence of subsequent fractures in patients with type 2 diabetes.

In women, the incidence of fractures at any site was predicted by their baseline FRAX score and was shown to be increased independently by the administration of pioglitazone. If the FRAX score is elevated by 10, the HR would be 1.044 (Table 4) to the 10th power, or 1.54, and with initiation of pioglitazone, the risk would be further elevated by 1.59 times (Table 4). It is known that pioglitazone prevents major adverse cardiovascular events, myocardial infarction, and stroke, but increases heart failure (32). Therefore, an optimal balance should be ensured carefully between its antidiabetic efficacy, effects on cardiovascular outcomes, and associated risk of fractures, when administration of pioglitazone is considered in women, especially with a high FRAX score.

### Table 5. Fracture Sites in Both Sexes

| Site                                      | Men (n = 121) | Women (n = 147) |
|-------------------------------------------|---------------|-----------------|
| Major osteoporotic                        | 24 (19.8%)    | 44 (29.9%)      |
| Humerus or forearm                        | 12 (9.9%)     | 31 (21.1%)      |
| Clinical spine (compression fracture)     | 8 (6.6%)      | 13 (8.8%)       |
| Proximal femur                            | 4 (3.3%)      | 0 (0.0%)        |
| At other sites                            | 97 (80.2%)    | 103 (70.1%)     |
| Finger                                    | 8 (6.6%)      | 13 (8.8%)       |
| Other sites of upper extremity            | 1 (0.8%)      | 1 (0.7%)        |
| Femur (not proximal) or lower limb        | 16 (13.2%)    | 16 (10.9%)      |
| Toe                                       | 13 (10.7%)    | 27 (18.4%)      |
| Other sites of lower extremity            | 9 (7.4%)      | 15 (10.2%)      |
| Rib                                       | 24 (19.8%)    | 18 (12.2%)      |
| Spine (except compression fracture)       | 6 (5.0%)      | 3 (2.0%)        |
| Pelvis                                    | 1 (0.8%)      | 1 (0.7%)        |
| Skull                                     | 5 (4.1%)      | 0 (0.0%)        |
| Others                                    | 14 (11.6%)    | 9 (6.1%)        |

Sites of the first fracture in men and women during the intervention period.
The present study confirms that the risk of fractures at any site is elevated with the use of TZDs in women with type 2 diabetes, in accordance with previous large-scale clinical trials and the guideline (3,12-15), and the elevated risk is considered to be attributed mainly to the elevated risk of osteoporotic fractures.

We also show that the FRAX score (major osteoporotic), which was shown to predict the absolute risk of major osteoporotic fractures in women of the general population in Japan (33), serves as a good predictor of the relative incidence of fractures in women with type 2 diabetes, even without the recently proposed adjustment for diabetes (3). Moreover, women with type 2 diabetes and a high FRAX score are exposed to higher risk of not only osteoporotic fractures but also non-osteoporotic fractures, and the existence of a potential threshold of the FRAX score is implied for non-osteoporotic fractures.

It was also shown in our study that the FRAX score was not associated with the incidence of fractures at any site in men, contrary to an earlier report in the general population in Japan (34). In our study, history of smoking at baseline was the only predictor of fractures at any site in men and the risk was almost doubled. It is known that history of smoking enhances the risk of not only osteoporotic fractures but also fractures at any site, partly via lowered BMD (35), whose association with the incidence of vertebral and non-vertebral fractures was recently reported even in elderly males with diabetes (36, 37). The effect of smoking on bone loss is likely to be larger in men than in women (35), and smoking cessation is recommended in the recent guideline (3), although it was also reported that the risk of fractures remained high in ex-smokers, especially men, for 5 years after smoking cessation (38).

We confirmed that the ratio of major osteoporotic fractures to total fracture events was not affected by the intensive therapy of the J-DOT3 study, in which glucose, blood pressure, and lipids were improved without a weight reduction, in both sexes: 22 out of 69 events (31.9%) in women in the conventional therapy group, 22 out of 78 (28.2%) in women in the intensive therapy group, 11 out of 56 (19.6%) in men in the conventional therapy group, and 13 out of 65 (20.0%) in men in the intensive therapy group. This contrasts with the intensive lifestyle modification for weight loss of the Look AHEAD study, which showed a 6.0% weight reduction from the baseline body mass index of 36 kg/m² (on average) and was associated with an increase in frailty fractures without an increase in all fractures (21).

Major osteoporotic fractures were reported to have occurred in 5.8% (39 out of 670) of the women who had their FRAX score evaluated during the 7.8 years in this study, which was lower than the mean FRAX score or the expected incidence (12.8%/10 years) by approximately 40%. In men, major osteoporotic fractures were reported in 2.0% (21 of 1043) during the 7.8 years, which was about one-third of the mean FRAX score (7.7%/10 years). These results differed from previous studies that demonstrated that the FRAX score underestimated the incidence of fractures in patients with type 2 diabetes in population-based cohorts which included nondiabetic subjects and in which fracture events were actively surveyed as the main outcome (5, 6), as opposed to the present clinical trial which took place at institutions that had diabetes care clinics and in which self-reported fracture events were surveyed as adverse events. The accuracy of the FRAX score in predicting the absolute risk may vary depending on the clinical setting.

### Table 6. Cox Regression Analysis of Major Osteoporotic Fractures and Fractures at Other Sites in Women

| Major osteoporotic fractures | Hazard ratio | 95% CI | P Value |
|-----------------------------|--------------|--------|---------|
| FRAX at baseline [%/10 years] | 0-10 / 10-20 | 1.902 | 0.851 4.251 | 0.117 |
| FRAX at baseline [%/10 years] | 0-10 / 20-30 | 2.402 | 0.973 5.930 | 0.057 |
| FRAX at baseline [%/10 years] | 0-10 / 30-40 | 4.327 | 1.189 15.743 | 0.026 |
| Administration of pioglitazone at 1 year | No / Yes | 1.873 | 0.948 3.701 | 0.071 |

| Fractures at other sites | Hazard ratio | 95% CI | P Value |
|-------------------------|--------------|--------|---------|
| FRAX at baseline [%/10 years] | 0-10 / 10-20 | 0.934 | 0.515 1.691 | 0.821 |
| FRAX at baseline [%/10 years] | 0-10 / 20-30 | 2.203 | 1.236 3.927 | 0.007 |
| FRAX at baseline [%/10 years] | 0-10 / 30-40 | 2.991 | 1.146 7.805 | 0.025 |
| Administration of pioglitazone at 1 year | No / Yes | 1.319 | 0.807 2.157 | 0.270 |

Cox regression analysis of fracture events 1 year after randomization was performed with potential prognostic factors in women, the categorized FRAX scores at baseline and administration of pioglitazone at 1 year, as covariates. The patients were excluded in whom (1) the FRAX score at baseline was missing, or (2) a major osteoporotic fracture event or a fracture event at other sites was reported within the first year after randomization. 668 women were subjected to the analysis of major osteoporotic fractures, and 661 women were to the analysis of fractures of other sites. HR to the control category shown left to the slash.
and data collection method, and thus needs to be more closely examined in future studies.

Although poor glycemic control is among the classical risk factors for fractures in patients with diabetes (1, 2, 8), neither HbA1c nor fasting glucose at baseline was associated with the incidence of fractures in our study, consistent with the results of a recent case-control study conducted in the United Kingdom (39). Furthermore, neither hypoglycemia nor hypotension was associated with the incidence. It should also be noted that severe hypoglycemia, another risk factor for fractures, possibly via an increase in falls (14, 40), was not frequently seen in either group in our study (4 and 7 episodes in the conventional therapy group and the intensive therapy group, respectively, during the 8.5 years) (27). Such care of diabetes in the J-DOIT3 study could have contributed to the lower incidence of fractures at any site (10.6% in total of both groups during the 7.8 years), compared with that (6.1% in total of both groups during 2.5-4 years) in a preceding prospective randomized parallel-group trial in Japan which was run from 2002 through to 2006 with comparable mean age at baseline (58 years) and a comparable ratio of women (37%-38%) (24).

One of the limitations of the present study is that occurrence of fractures was reported as an adverse event, not as a primary or secondary outcome, and thus some fractures may not have been reported as such in some patients. Besides, falls without clinical significance were not reported as adverse events, and thus it was not clear how intensive multifactorial intervention affected the incidence of falls, which are known to be associated with fractures (8). Moreover, the medications used for osteoporosis treatment that could affect the incidence of fractures were not examined.

As for the FRAX score, it was obtained in less than 70% of the patients and may have been underestimated in a portion of them due to the presence of some components, such as family history of hip fracture and comorbid secondary osteoporosis, which may not have been amenable to retrospective analysis. Moreover, the FRAX score with BMD at baseline might have been better to predict the incidence of fractures.

Despite these limitations, the present study has shown a lack of significant association between the intensified multifactorial intervention of the J-DOIT3 study and risk of fractures. It has also provided evidence for the risk predictors identified, and currently, a postintervention follow-up study of the J-DOIT3 trial is underway, with fractures as one of the exploratory outcomes (30).

In conclusion, the intensified multifactorial intervention is not associated with an increased risk of fractures in patients with type 2 diabetes. The risk of fractures is expected to be higher in men with type 2 diabetes who have a history of smoking, whereas the risk is predicted by the FRAX score and independently elevated by administration of pioglitazone in women with type 2 diabetes.

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Author Contributions: T.S. steered the study, researched data, and wrote the manuscript. K.U. designed the protocol, steered the study, researched data, and wrote the manuscript. K.M. and Y.Ok. steered the study and researched data. Y.T. designed the protocol on evaluation of fracture risk. Y.Oh. and M.N. designed the protocol, steered the study, and researched data. T.K. designed the protocol, steered the study, researched data, and reviewed/edited the manuscript.

Collaborators for the J-DOIT3 Study

Asahikawa Medical University, Asahikawa, Hokkaido:
Masakazu Haneda. Yoshida Hospital, Asahikawa, Hokkaido:
Yasunori Iwashima. Hiroaki University Hospital, Hiroaki, Aomori:
Toshihiro Suda, Naoki Tamasawa, and Makoto Daimon. Iwate Medical University Hospital, Morioka, Iwate: Jo Satoh, Noriko Takebe, and Yasushi Ishigaki. Fukushima Medical University, Fukushima, Fukushima: Tsuyoshi Watanabe, and Hiroaki Satoh. Dokkyo Medical University, Mibu, Tochigi: Kikuo Kasai, and Yoshimasa Aso. Jichi Medical University, Shimotuku, Tochigi: Shun Ishibashi. Saitama Medical University Hospital, Moroyama, Saitama: Shigehiro Katayama. Jichi Medical University Saitama Medical Center, Saitama, Saitama: San-e Ishikawa, and Masafumi Kakei. Saitama Red Cross Hospital, Saitama, Saitama: Kazuyuki Namai. Asahi General Hospital, Ashahi, Chiba: Naotake Hashimoto, Yoshifumi Suzuki, and Shunichiro Onishi. Chiba University Hospital, Chiba, Chiba: Koutaro Yokote. Kameda Medical Center, Kamogawa, Chiba: Masafumi Matsuda, and Masahiro Masuzawa. Memorial Hospital of Kazusa, Kisarazu,
Chiba: Mitsutaka Motoyoshi, Nihon University Itabashi Hospital, Itabashi, Tokyo: Yoichi Hayashi, Satoshi Saito, Norikazu Ogihara, and Hisamitsu Ishihara. The Jikei University School of Medicine, Minato, Tokyo: Naoko Tajima, and Kazunori Utsunomiya. Keio University School of Medicine, Shinjuku, Tokyo: Akira Shimada, and Hiroshi Itoh. Japanese Red Cross Medical Center, Shibuya, Tokyo: Toru Hiyoshi. Juntendo University Graduate School of Medicine, Bunkyo, Tokyo: Ryuzo Kamowari, and Hirotaka Watada. NTT Medical Center Tokyo, Shinagawa, Tokyo: Michio Hayashi. Federation of National Public Service Personnel Mutual Aid Associations, Toranomon Hospital, Minato, Tokyo: Yasumichi Morii. Mitsu Memorial Hospital, Chiyoda, Tokyo: Teruo Shiba, and Akihiro Isoyama. Tokyo Women's Medical University Hospital, Shinjuku, Tokyo: Hiroshi Sakura. Tokyo Medical University Hospital, Shinjuku, Tokyo: Masato Odawara. The University of Tokyo Hospital, Bunkyo, Tokyo: Kazuyuki Tobe, Kazuhisa Tsukamoto, and Yoshimasa Yamauchi. Teikyo University School of Medicine Hospital, Itabashi, Tokyo: Tamio Teramoto. Tokyo Medical and Dental University, Tokyo Medical Center, Bunkyo, Tokyo: Yukio Hirata, Isao Uchimura, and Yoshihiro Ogawa. Toho University Medical Center, Omori Hospital, Ota, Tokyo: Gen Yoshino, and Takanishi Hirose. National Center for Global Health and Medicine Hospital, Shinjuku, Tokyo: Hiroshi Kajio. Saiseikai Central Hospital, Minato, Tokyo: Yoshihito Atsumi, Akira Shimada, and Yoichi Oikawa. Tokyo Metropolitan Geriatric Hospital, Itabashi, Tokyo: Atsushi Araki. Hachioji Medical Center of Tokyo Medical University, Hachioji, Tokyo: Akio Ueki, and Atsushi Ohno. Showa General Hospital, Kodaira, Tokyo: Masafumi Kitaoka. Kitasato University Hospital, Saginagara, Kanagawa: Yoshikuni Fujita, Tatsuo Moriya, Taiko Tojo, and Masayoshi Shichiri. St. Marianna University School of Medicine, Kawasaki, Kanagawa: Yasushi Tanaka. Tokai University School of Medicine, Isehara, Kanagawa: Daisuke Suzuki, and Masayo Toyoda. Shonan Kamakura General Hospital, Kamakura, Kanagawa: Kumiko Hamano, and Rieko Komi. Yokohama City University Hospital, Yokohama, Kanagawa: Yasuo Terauchi. Yokohama Sakaekyosai Hospital, Federation of National Public Service Personnel Mutual Associations, Yokohama, Kanagawa: Nobuki Kuzuya, and Masayo Yamada. Odawara Municipal Hospital, Odawara, Kanagawa: Tadahisa Momoki, and Koichiro Sato. Yaizu City Hospital, Yaizu, Shizuoka: Atsumi Murao. Kanazawa University Hospital, Kanazawa, Ishikawa: Toshinari Takamura. Nagano Chuo Hospital, Nagano, Nagano: Hiroaki Yamamoto. Ogaki Municipal Hospital, Ogaki, Gifu: Hiroshi Sobajima. Gamagori City Hospital, Gamagori, Aichi: Akihiko Yoneyama, and Kenichi Itô. Chukyo Hospital, Nagoya, Aichi: Hiroshi Tanaka, and Masayuki Hayashi. Nagoya Medical Center, Nagoya, Aichi: Yasuhisa Kato. Fujita Health University Hospital, Toyoake, Aichi: Mitsuyasu Itoh, and Atsushi Suzuki. Chubu Rosai Hospital, Nagoya, Aichi: Mikihito Nakayama, Takahisa Sanoy, and Eitaro Nakashima. Miyazaki University Hospital, Tsu, Mie: Yasuhiro Sumida, and Yutaka Yano. National Hospital Organization Mie Chuo Medical Center, Tsu, Mie: Tsusayoshi Tanaka. Ise Red Cross Hospital, Ise, Mie: Kazuya Murata. Shiga University of Medical Science, Otsu, Shiga: Atsunori Kashiwagi, and Hiroshi Maegawa. National Hospital Organization Kyoto Medical Center, Kyoto, Kyoto: Shigeo Kono. Kyoto University Hospital, Kyoto, Kyoto: Nobuya Inagaki. Osaka Police Hospital, Osaka, Osaka: Keisuke Kosugi, and Tetsuyuki Yasuda. National Cerebral and Cardiovascular Center, Suita, Osaka: Yasunao Yoshimasa, and Ichiro Kishimoto. Osaka City General Hospital, Osaka, Osaka: Toshiki Sato, and Masayuki Hosoi. Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Osaka: Tomoyuki Yamashita. Osaka University Hospital, Suita, Osaka: Munehide Matsushita, and Iichiro Shimomura. Kansai Electric Power Hospital, Osaka, Osaka: Ataru Taniguchi, Akira Kuroe, and Takeshi Kurose. Kindai University Faculty of Medicine, Osakasayama, Osaka: Hiroshi Ikegami. Kobe University Graduate School of Medicine, Kobe, Hyogo: Takeshi Ohara, and Kazukiho Sakaguchi. Hyogo College of Medicine College Hospital, Nishinomiya, Hyogo: Mitsuyoshi Namba, Seimeikai Ikeda Hospital, Amagasaki, Hyogo: the late Masaki Ikeda, and Hiroki Ikeda. Kawasaki Medical School Hospital, Kurashiki, Okayama: Kohei Kaku, Kurashiki Central Hospital, Kurashiki, Okayama: Kenji Takahashi. Okayama University Hospital, Okayama, Okayama: Hirofumi Makino. Saito Central Hospital, Saito, Ehime: Masazumi Fujiwara. Ehime Prefectural Central Hospital, Matsuyama, Ehime: Ikki Shimizu, Keizo Ono, and Osamu Ebisu. Yamaguchi University Hospital, Ube, Yamaguchi: Yukio Tanizawa. University of Occupational and Environmental Health, Kitakyushu, Fukuoka: Yosuke Okada. Iizuka Hospital, Iizuka, Fukuoka: Shoichi Natori, Takehiko Kodera, Naoichi Sato, and Makoto Ide. Kurume University Hospital, Kurume, Fukuoka: Kentaro Yamada. Fukuoka City Medical Association Hospital, Fukuoka, Fukuoka: Fumio Umeda, Shoichi Natori, Tomoaki Eto, Katsuo Mimura, Shin sugi Hiramatsu, Tomoaki Inoue, and Ryoko Takei. National Hospital Organization Kyushu Medical Center, Fukuoka, Fukuoka: Atsushi Ogo. Nagasaki University Hospital, Nagasaki, Nagasaki: Katsumi Eguchi, Eiji Kawasaki, and Yuji Koide. Kumamoto University Hospital, Kumamoto, Kumamoto: Eiichi Araki. Jinnouchi Hospital Diabetes Care Center, Kumamoto, Kumamoto: Hideaki Jinnouchi. The Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Nagasaki: Yasuo Ueda. University of Miyazaki Hospital, Miyazaki, Miyazaki: Masami Nakazato. List of Safety Assessment Committee Members: Shigeru Kageyama (chair), Hiroshi Sakura, Masato Matsushima, and Yuichiro Yamada.

Additional Information

Correspondence: Takashi Kadowaki, M.D., Ph.D., Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, 7-3-1 Honjo, Bunkyo-ku, Tokyo 113-8655 Japan. Email: kadowaki-3im@h.u-tokyo.ac.jp.

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