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1 **Ten years change in post fracture care for hip fracture patients**

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5 **Conflict of Interest:** Shun Shimodan, Dai Sato, Kaname Takahashi, Ryosuke Hishimura,

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8 Iwasaki, Tomohiro Shimizu declare that they have no conflict of interest.

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11

1 **Abstract**

2 *Purpose*

3 This multi-center, retrospective study aimed to clarify the changes in postoperative care
4 provided by orthopaedic surgeons after hip fractures and clarify the incidence of secondary
5 fractures requiring surgery.

6 *Methods*

7 Subjects were patients with hip fracture treated surgically in seven hospitals during the 10-
8 year period from January 2008 to December 2017. Data on patient demographics,
9 comorbidities, preoperative and postoperative osteoporosis treatments, and secondary
10 fractures were collected from the medical records.

11 *Results*

12 In total, 4764 new hip fractures in 982 men and 3782 women (mean age: 81.3 ± 10.0 years)
13 were identified. Approximately 10% of patients had a history of osteoporosis drug treatment
14 and 35% of patients received postoperative drug treatment. The proportion of patients
15 receiving postoperative drug therapy increased by approximately 10% between 2009 and
16 2010, 10% between 2010 and 2011, and 10% between 2011 and 2013. Although the rate of
17 secondary fractures during the entire period and within 3 years decreased from 2011, the rate
18 of secondary fracture within 1 year remained at around 2% every year.

19 *Conclusions*

20 The approval of new osteoporosis drugs and the establishment of osteoporosis liaison
21 services have had a positive effect on the use of postoperative drug therapy in the orthopedic
22 field. Our finding that the rate of secondary fracture within 1 year of the initial fracture
23 remained around 2% every year, despite improvements in postoperative drug therapy,
24 suggests that both rehabilitation for preventing falls and early postoperative drug therapy are
25 essential to prevent secondary fractures.

1 **Keywords:** hip fracture, secondary fracture, anti-osteoporosis therapy, osteoporosis liaison

2 service

3

1 **Introduction**

2 Hip fractures are associated with increased morbidity, functional decline, and death
3 in older adults, as well as increased use of health care services in most industrialized
4 countries [1,2]. It is estimated that the number of hip fractures worldwide will rise from 1.7
5 million in 1990 to 6.3 million in 2050 [3]. In particular, given that three-quarters of the
6 world's population lives in Asia, it is projected that Asian countries will contribute more to
7 the pool of hip fractures in the coming years. By 2050, more than 50% of all osteoporotic
8 fractures will occur in Asia [4,5]. According to a nationwide survey of hip fractures in Japan,
9 the total number of patients who experienced a hip fracture in 2012 was 175,700 (men,
10 37,600; women, 138,100), which represents an increase from 2007 (total, 148,100; men,
11 31,300; women, 116,800) [6,7]. The annual costs of medical and nursing care associated with
12 osteoporotic fractures have been estimated to be JPY 797.4 to 989.5 billion (US\$7.974 to
13 9.895 billion; US\$1=JPY100) in Japan [8] and are expected to rise in parallel with the
14 increase in the incidence of osteoporotic fractures.

15 Patients with hip fractures have a 2.5-fold increased risk of secondary fractures
16 compared to age-matched persons without previous fractures [9]. More specifically, patients
17 who have sustained one hip fracture have a higher risk of a contralateral hip fracture
18 compared to the general populations [10], and second hip fractures often occur within 1 year
19 of initial fractures [11,12]. Treatment with anti-osteoporosis drugs is essential for patients
20 after their initial fracture, as a first fracture is the highest risk factor for a second fracture
21 [13,14]. Nevertheless, data suggest that few patients with hip fracture actually received
22 pharmacologic therapy for osteoporosis [15-18]. Therefore, poor persistence with
23 osteoporosis treatments is a global public health problem.

24 Recently, various anti-osteoporosis drugs have been developed and are available on
25 the market. In Japan, teriparatide (TPD), recombinant human parathyroid hormone (1-34),

1 and denosumab (DSMAB), a fully human monoclonal antibody that binds the cytokine
2 receptor activator of NFκB ligand (RANKL), were approved in 2010 and 2013, respectively.
3 Additionally, based on the fracture liaison services (FLS) [19,20], a coordinator-based
4 secondary fracture prevention service developed in the United Kingdom, the osteoporosis
5 liaison service (OLS) was established in Japan in 2012 as a comprehensive care system for
6 osteoporosis. On the contrary, in Japan, hip fractures are usually treated by orthopedic
7 surgical procedures and followed with postoperative therapy by the same orthopedic surgeon,
8 not a physician specializing in osteoporosis treatment. Therefore, it is of great importance to
9 assess how postoperative care after hip fracture that is provided by an orthopedic surgeon has
10 changed now that various anti-osteoporosis drugs have been approved and the OLS has been
11 established.

12 The objectives of this multi-center retrospective study were to investigate the rate of
13 postoperative care change after hip fracture and the incidence of secondary fractures
14 requiring surgery. The hypothesis of this study is that development of anti-osteoporosis drugs
15 and dissemination of knowledge about treatment for osteoporosis among surgeons has
16 improved the treatment rate for bone fragility and the prevention of secondary fractures.

17

18 **Methods**

19 This study was designed as a retrospective, registry-based, uncontrolled, follow-up
20 study. This study was approved by the local ethics committee at the Hokkaido University
21 Hospital (017-0448) and by each participating hospital. A total of 4803 hip fracture patients
22 treated with surgery at seven hospitals that function as base hospitals in regional cities in
23 Hokkaido prefecture in Japan during the 10-year period from January 2008 to December
24 2017 were included. Data were collected from medical records. Thirty-nine patients who
25 were younger than 50 years were excluded. Finally, 4764 patients (male, 982; female, 3782)

1 were included in this current study. Three of the seven hospitals carried out OLS.

2 Data on patient demographics including age, sex, and body mass index (BMI),
3 comorbidities including diabetes mellitus (DM), chronic obstructive pulmonary disease
4 (COPD), malignant tumor, and rheumatoid arthritis, and glucocorticoid use, preoperative
5 medical history for osteoporosis drugs including bisphosphonate (BP), selective estrogen
6 receptor modulator (SERM), TPD and DSMAB, and calcium (Ca) or active vitamin D3
7 preparation at surgery were collected from their medical records. Data on postoperative
8 osteoporosis treatment, osteoporosis inspection (dual energy x-ray absorptiometry),
9 outpatient visits after discharge, the occurrence of a secondary fracture (contralateral hip
10 fracture, distal radial fracture and proximal humerus fracture) requiring surgery, and follow-
11 up period after the initial surgery were also collected from medical records.

12 Chi-squared or independent t-tests were used to compare differences in subject
13 demographics. The incidence of secondary fracture was estimated by the Kaplan-Meier
14 method, and differences were investigated by the log-rank test among the patients who could
15 be followed. All statistical analyses were performed using SPSS Statistics version 23.0 (IBM
16 Corporation, Armonk, NY) with a significance level set at 0.05.

17

18 **Results**

19 *Patient demographics and osteoporosis care during the whole period*

20 In this study, the number of the hip fractures treated with the surgery in this study
21 gradually increased during the entire period (Fig.1). Table 1 shows a summary of patient
22 demographics. Male patients with hip fracture were significantly younger than the female
23 patients ($P<0.001$). A significantly higher proportion of male patients experienced COPD and
24 malignant tumors compared to female patients ($P<0.001$). In contrast, a significantly higher
25 proportion of female patients experienced rheumatoid arthritis (RA) compared to male

1 patients (P=0.024). Preoperatively, 8.4% of patients underwent osteoporosis drug therapy and
2 6.3% took active vitamin D3 or Ca preparations. Postoperatively, 13.0 % of patients
3 underwent osteoporosis inspection, 34.2% underwent osteoporosis drug therapy, and 12.6%
4 took active vitamin D3 or Ca preparations. A significantly lower proportion of male patients
5 underwent preoperative and postoperative inspection and therapy compared to female
6 patients (P<0.001). Postoperatively, 35.7% of patients attended outpatient visits after
7 discharge, 4.1% sustained a secondary fracture, and 2.0% had a secondary fracture within 1
8 year of the initial fracture. The mean follow-up period was 25.8 months. There were no
9 significant differences in these parameters between male and female patients.

10 Patients who underwent preoperative drug therapy were older than those who did
11 not (P<0.001) (Table 2). Significantly more patients who underwent preoperative
12 osteoporosis drug therapy experienced RA and used glucocorticoid steroids (GCs) compared
13 to those who did not (P<0.001). The proportion of patients who underwent postoperative
14 osteoporosis inspection, took active vitamin D3 or Ca preparations, and attended outpatient
15 visits after discharge was higher in patients who received preoperative drug therapy
16 compared to those who did not (P<0.001). Although 1278 patients of 4360 patients (29.3%)
17 who did not receive preoperative therapy started drug therapy postoperatively, 51 patients of
18 404 patients (12.2%) who received preoperative therapy did not continue drug therapy. No
19 differences in the incidence of secondary fracture and secondary fracture within 1 year and 3
20 years, or the duration between the initial and secondary fractures were found in patients who
21 underwent preoperative drug therapy and those who did not.

22 *Changes in postoperative osteoporosis care over time (2008-2017)*

23 The proportion of patients who received postoperative osteoporosis drug therapy
24 increased by approximately 10% from 2010 (when TPD was approved), 2011 and 2013
25 (when DSMAB was approved) compared with their proportion in the preceding (Fig. 2). The

1 proportion of patients who received preoperative osteoporosis drug therapy was around 5%.
2 The majority of the postoperative drug therapy involved BP (over 80%) (Fig. 3). The
3 proportion of TPD and DSMAB administration increased slowly after approval. On the
4 contrary, the proportion of postoperative osteoporosis inspection and outpatient visits after
5 discharge increased gradually from 2014 (Fig. 2). The proportion of patients who took Ca or
6 active vitamin D3 was 5%-10% until 2012, increased gradually and reached around 20% in
7 2017. One hospital started OLS from 2012 and the other two hospitals started it from 2015.
8 There were totally 1295 patients who received OLS. The hospitals operating OLS exhibited
9 higher proportion of postoperative therapy compared to those without OLS (Fig. 4).

10 *Efficacy of postoperative osteoporosis drug therapy*

11 Patients who received postoperative drug therapy were significantly more likely to
12 have received preoperative drug therapy and take Ca or active vitamin D3 preparations
13 compared to those who did not receive postoperative drug therapy (Table 3). Of the 1631
14 patients who received postoperative osteoporosis drug therapy, 509 patients (31.2%)
15 underwent postoperative inspection, and 728 patients (44.6 %) attended outpatient
16 appointments after discharge. These proportions were significantly higher compared to
17 patients who did not receive postoperative drug therapy. On the contrary, no significant
18 differences in the occurrence of secondary fractures, occurrence of secondary fractures within
19 1 year of the initial fracture, or duration between initial and secondary fractures were noted in
20 patients who had received postoperative drug therapy and those who had not.

21 The 120-month cumulative incidence of secondary fracture was estimated to be
22 23.9% in patients with postoperative therapy and 32.5% in those without postoperative
23 therapy, with a difference between the two groups, albeit not statistically significant
24 ($P=0.057$, log-rank test) (Fig. 5). Although the prevalence of secondary fractures during the
25 whole period and within 3 years of initial surgery decreased from 2011, the prevalence of

1 secondary fractures occurring within 1 year was around 2% every year (Fig. 6). No
2 significant differences in the occurrence of secondary fractures, occurrence of secondary
3 fractures within 1 year of the initial fracture, or duration between initial and secondary
4 fractures were found in patients who had received postoperative Ca or active vitamin D3
5 preparations and those who had not.

6

7 **Discussion**

8 This multicenter retrospective study addressed the changes in approaches to
9 postoperative osteoporosis treatment. The finding of this current study that the total number
10 of hip fractures increased over 10 years is consistent with the overall trend of increase due to
11 the aging population in Japan [21]. Although the majority of the postoperative drug therapy
12 involved bisphosphonate over the whole period, the proportion of patients undergoing
13 postoperative drug therapy and inspection and the number of patients attending outpatient
14 visits after discharge increased gradually. Considering that the proportion of the secondary
15 fracture within 3 years clearly decreased from 2011, when the proportion of the postoperative
16 drug therapy got increased, the improvement of the postoperative therapy could be
17 considered to have a positive effect for preventing the secondary fracture.

18 The increase in the proportion of drug therapy demonstrated in this study is
19 consistent with the recent Japanese report [22], suggesting that orthopedic surgeons are
20 promoting awareness of osteoporosis interventions after the first fragility fractures much
21 better. In North America, several studies have recommended that the orthopedic surgeon
22 directly treating the fracture should perform a BMD examination and forward the results to
23 the primary care physician following the course of osteoporosis treatment [23-25].
24 Additionally, Miki et al. showed improved rates of early osteoporosis drug treatment
25 following hip fractures when osteoporosis education was initiated by the treating orthopedic

1 surgeon while the patient is still in the hospital and the treatment is initiated in an orthopedic
2 osteoporosis clinic [25]. The main limitation of this multicenter retrospective therapy was
3 that the time of starting OLS and insurance medical treatment system, such as on diagnosis
4 procedure combination system, vary with each hospital. The finding of this study that almost
5 all postoperative therapy in the entire period was BP and TPD and DSMAB might not
6 contribute directly to the increase in postoperative therapy as expected might be affected by
7 the medical care system in Japan. However, considering that the rates of postoperative
8 osteoporosis drug therapy increased by approximately 10% in 2010, 2011, and 2013 and the
9 differences in the proportions of postoperative therapy between hospitals with and without
10 OLS, the approval of new osteoporosis drugs and the establishment of OLS programs could
11 have a further positive effect on the administration of postoperative drug therapy in patients
12 with the hip fracture. The finding of this study that the proportion of the postoperative
13 osteoporosis inspection has risen since 2014 could also be considered to be the effect of OLS.

14 Our finding that postoperative drug therapy showed a trend to reduce the secondary
15 fracture is consistent to the previous prospective cohort studies about the efficacy of
16 bisphosphonate for preventing a secondary hip fracture [26,27]. Because less than half of the
17 patients who received postoperative drug therapy attended outpatient visits after discharge in
18 this study, the discrepancy of efficacy for preventing the secondary fracture between this
19 study and these previous prospective cohort studies might be explained by the differences in
20 follow-up rate, as well as the study design. More specifically, the proportion of patients
21 undergoing postoperative drug therapy was higher than the proportion of patients who
22 attended outpatient appointments after discharge between 2011 and 2013, suggesting that the
23 continuation of postoperative drug therapy might be more difficult in Japan compared to in
24 the immediate postoperative period. Because the prescription of anti-osteoporosis therapy
25 medications in rehabilitation hospitals is limited in Japan, modification of the care system as

1 well as osteoporosis education for orthopedic surgeons might be necessary for prevention of
2 secondary fractures.

3 Our finding that half of patients with a secondary fracture experienced that fracture
4 within 1 year of the initial hip fracture is consistent with the previous reports about the
5 incidence of secondary hip fracture [28-30]. The reason for the transient marked increase in
6 risk is not known, but immobilization and impaired coordination are potential factors [31,32].
7 In contrast, our finding that the rate of secondary fracture within 1 year after the initial
8 fracture remained around 2% every year, regardless of improvements in postoperative drug
9 therapy, is contrary to the conclusion of the recent large cohort studies that reported
10 immediate treatment after initial fracture can prevent a higher number of new fractures
11 compared to when treatment is delayed [33,34]. The discrepancy between this current study
12 and other reports might be explained by a limitation of this study that we did not include all
13 secondary fractures, but only those treated surgically. Considering Lyles's report that there
14 was no difference in new hip fracture occurrence within 1 year of the surgery [26],
15 rehabilitation for preventing fall in addition to early postoperative drug therapy after surgery
16 is essential for secondary fracture prevention.

17 Several other limitations need to be considered when interpreting the results of this
18 study. First, in this study, patients who received BP therapy were not divided according to
19 alendronate, risedronate, minodronate, ibandronate, and zoledronate therapy. Given the
20 possibility of differences in adherence and absorptivity of each drug, future studies should
21 address the efficacy and adherence of each individual drug. Second, because all data were
22 collected retrospectively from medical records, adherence to therapy could not be
23 investigated. Third, other secondary fragility fractures such as distal radius, proximal
24 humerus, and lumbar vertebrae fractures that do not require surgery were not investigated.
25 Therefore, future prospective studies that focused on specific therapies might be necessary.

1 Fourth, this study did not include dementia as a comorbidity. Dementia has reported to be a
2 strong risk factor for hip fracture. In addition, the presence of dementia is expected to disturb
3 the follow-up, nutritional instruction, and treatment compliance in osteoporotic patients.
4 Fifth, although the participating hospitals were main hospitals in their cities, patients who
5 received therapy from other hospitals in the same area may have been included.

6 **Conclusion**

7 Over the study period, the proportion of patients receiving postoperative drug
8 therapy and inspection, and attending outpatient visits after discharge increased gradually in
9 the north side of Japan. The approval of new osteoporosis drugs and establishment of OLS
10 programs could have a further positive effect on postoperative drug therapy in the orthopedic
11 field. Our finding that the proportion of secondary fractures within 1 year of the initial
12 fracture remained around 2% every year, despite improvements in postoperative osteoporosis
13 drug therapy, suggests that rehabilitation for preventing falls as well as early postoperative
14 drug therapy after surgery, are essential for secondary fracture prevention.

15

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20

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6

1 **Table 1** Summary of patient demographics, comorbidities, and preoperative and
 2 postoperative treatment according to sex

	Total (N=4764)	Male (N=982)	Female (N=3782)	P-value
Age (years)	81.3 (10.0)	78.0 (10.6)	82.2 (9.6)	<0.001
BMI (kg/m ²)	21.1 (3.9)	21.2 (3.5)	21.1 (4.0)	0.486
Comorbidities				
DM	981 (20.6%)	210 (21.4%)	771 (20.4%)	0.490
CKD	1094 (23.0%)	232 (23.6%)	862 (22.8%)	0.580
COPD	213 (4.5%)	71 (7.2%)	142 (3.7%)	<0.001
Malignant tumor	585 (12.3%)	171 (17.4%)	414 (10.9%)	<0.001
RA	133 (2.8%)	17 (1.7%)	116 (3.1%)	0.024
GC use	136 (2.8%)	20 (2.5%)	116 (3.1%)	0.084
Preoperative				
Osteoporosis drug therapy	404 (8.4%)	26 (2.6%)	378 (10.0%)	<0.001
Ca or active Vit.D3 preparations	301 (6.3%)	29 (3.7%)	272 (7.2%)	<0.001
Postoperative				
Osteoporosis inspection	617 (13.0%)	96 (9.8%)	521 (13.8%)	0.001
Osteoporosis drug therapy	1631 (34.2%)	241 (24.5%)	1390 (36.8%)	<0.001
Ca or active Vit.D3 preparations	599 (12.6%)	79 (8.0%)	520 (13.7%)	<0.001
Outpatient visits after discharge	1701 (35.7%)	330 (33.6%)	1371 (36.3%)	0.123
Secondary fx	194 (4.1%)	37 (3.8%)	157 (4.1%)	0.585
Secondary fx within 3 years	145 (3.0%)	30 (3.1%)	115 (3.0%)	0.981
Secondary fx within 1 year	97 (2.0%)	23 (2.3%)	74 (2.0%)	0.516
Duration between fxs, (months)	21.1 (22.3)	14.9 (23.3)	22.6 (16.2)	0.061

3 BMI, body mass index; Ca, calcium; DM, diabetes mellitus; COPD, chronic obstructive
 4 pulmonary disease; CKD, chronic kidney disease; RA, rheumatoid arthritis; GC,
 5 glucocorticoid steroid; Vit.D3, vitamin D3; fx, fracture.

6

1 **Table 2** Summary of patient demographics, comorbidities, and preoperative and
 2 postoperative treatment according to use of preoperative osteoporosis drug therapy

	Preoperative (+) (N=404)	Preoperative (-) (N=4360)	P-value
Age (years)	83.3 (8.1)	81.2 (10.1)	<0.001
BMI (kg/m ²)	20.9 (4.1)	21.2 (3.3)	0.214
Comorbidities			
DM	64 (15.8%)	917 (21.0%)	0.014
CKD	90 (22.3%)	1004 (23.2%)	0.732
COPD	23 (5.7%)	190 (4.4%)	0.214
Malignant tumor	53 (13.1%)	532 (12.2%)	0.591
RA	27 (6.7%)	106 (2.4%)	<0.001
GC use	27 (6.7%)	109 (2.5%)	<0.001
Postoperative			
Osteoporosis inspection	87 (21.5%)	530 (12.2%)	<0.001
Osteoporosis drug therapy	353 (87.8%)	1278 (29.3%)	<0.001
Ca or active Vit.D3 preparations	120 (29.7%)	479 (11.0%)	<0.001
Follow-up	180 (44.6%)	1521 (34.9%)	<0.001
Secondary fx	19 (4.7%)	175 (4.0%)	0.504
Secondary fx within 3 years	18 (4.5%)	127 (2.9%)	0.084
Secondary fx within 1 year	13 (2.3%)	84 (2.0%)	0.338
Duration between fxs (months)	13.0 (11.9)	22.0 (23.0)	0.098

3 BMI, body mass index; Ca, calcium; DM, diabetes mellitus; CKD; chronic kidney disease,
 4 COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; GCs, glucocorticoid
 5 steroid; Vit.D3, vitamin D3; fx, fracture.

6

1 **Table 3** Summary of patient demographics, comorbidities, and preoperative and
 2 postoperative treatment according to use of postoperative osteoporosis drug therapy

	Postoperative (+) (N=1631)	Postoperative (-) (N=3133)	P-value
Preoperative			
Osteoporosis treatment	353 (21.6%)	51 (1.6%)	<0.001
Ca or active Vit.D3 preparations	168 (10.3%)	133 (4.2%)	<0.001
Postoperative			
Osteoporosis inspection	509 (31.2%)	108 (3.4%)	<0.001
Outpatient visits after discharge	728 (44.6%)	973 (31.1%)	<0.001
Secondary fx.	58 (3.6%)	136 (4.3%)	0.191
Secondary fx within 3 years	49 (3.0%)	96 (3.1%)	0.909
Secondary fx within 1 year	31 (1.9%)	66 (2.1%)	0.687
Duration for secondary fx, month	17.5 (18.9)	22.9 (23.5)	0.135

3 BMI, body mass index; Ca, calcium; DM, diabetes mellitus; CKD; chronic kidney disease,
 4 COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; GCs, glucocorticoid
 5 steroid; Vit.D3, vitamin D3; fx, fracture.

1 Figure legends

2 **Fig. 1** Longitudinal numbers of the hip fracture cases during the whole period

3 White circle, total patient number; black square, male patient number; black circle, female
4 patient number.

5

6 **Fig. 2** Longitudinal trends in postoperative osteoporosis care during the whole period

7 Black circle, proportion of patients who received preoperative drug therapy; white circle,
8 proportion of patients who received postoperative drug therapy; square, proportion of patients
9 who received postoperative inspection; triangle, proportion of patients who attended
10 outpatient appointments after discharge.

11 TPD; teriparatide, OLS; osteoporosis liaison service.

12

13 **Fig. 3** Longitudinal trends in postoperative osteoporosis drug therapy during the whole period

14 Black circle, proportion of patients who received postoperative bisphosphonate (BP) therapy;
15 white circle, proportion of patients who received postoperative selective estrogen receptor
16 modulator (SERM) therapy; square, proportion of patients who received postoperative
17 teriparatide (TPD) therapy; triangle, proportion of patients who received postoperative
18 denosumab (DSMAB) therapy.

19

20 Fig. 4 Longitudinal trends in the proportion of the postoperative therapy between hospitals
21 with and without OLS. OLS; osteoporosis liaison service

22

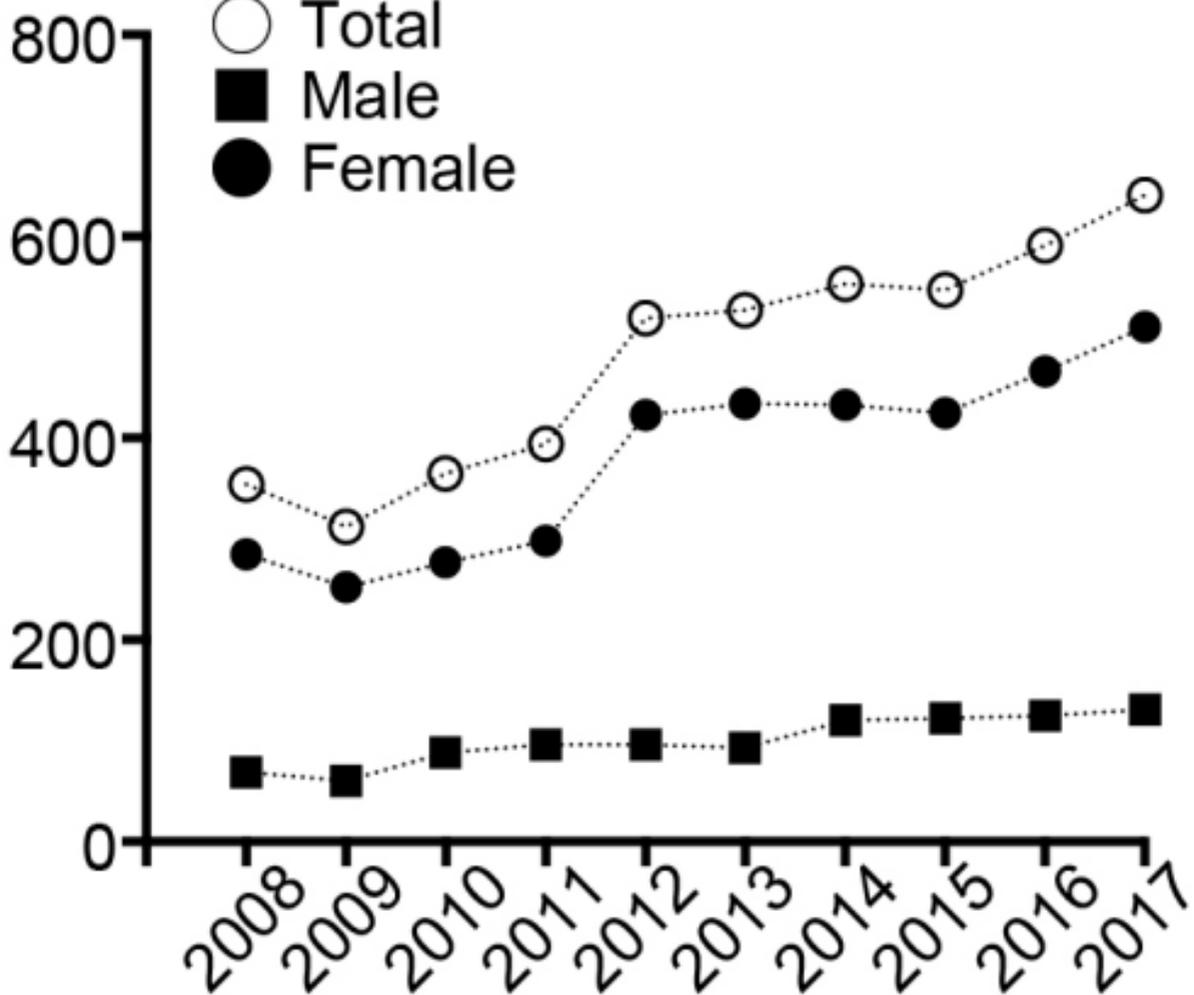
23 Fig. 5 Kaplan–Meier curves for the occurrence of secondary fracture between patients with
24 and without postoperative therapy

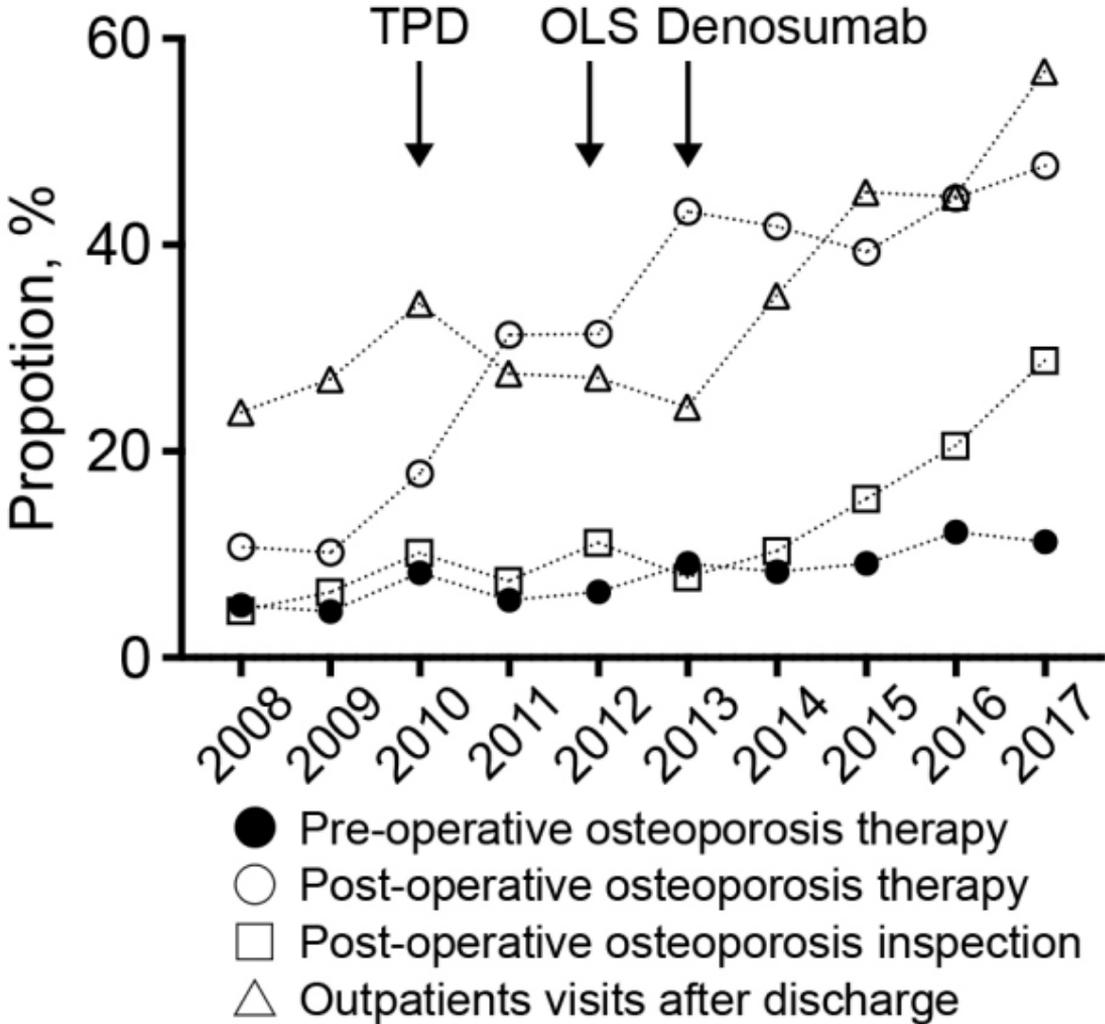
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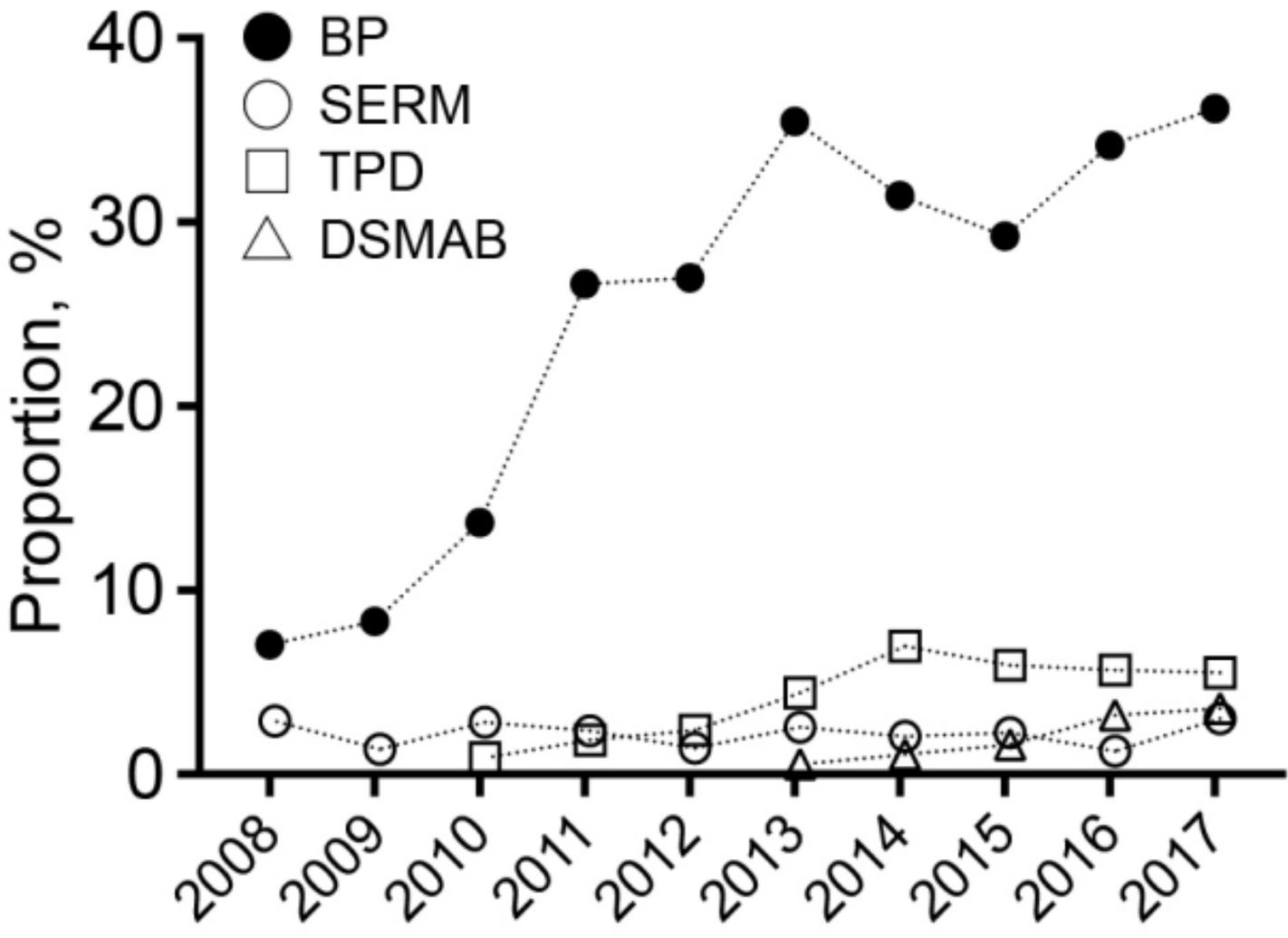
- 1 Fig. 6 Longitudinal trends in secondary fractures during the whole period
- 2 White circle, proportion of patients who sustained a secondary fracture; white square
- 3 proportion of patients who had a secondary fracture within 3 years of the initial hip fracture;
- 4 black circle, proportion of patients who suffered a secondary fracture within 1 year of the
- 5 initial hip fracture. Fx, fracture
- 6

Hip fracture, cases

- Total
- Male
- Female







Post-operative osteoporosis therapy

