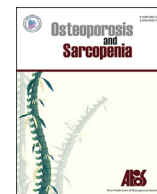




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## Original article

## The secular trends in the use of medications for osteoporosis in South Korea using Intercontinental Medical Statistics Health Sales Audit 2006–2018

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## ABSTRACT

**Objectives:** Osteoporosis medications are widely available in South Korea, and well reimbursed by the Government Health Insurance; however, some expensive drugs are not reimbursed. The prescription of anti-osteoporosis drugs (AODs) are increasing for the elderly and for postmenopausal women. We investigate the secular trends of AODs in South Korea.

**Methods:** We used the Intercontinental Medical Statistics Health Sales Audit between January 1, 2006 and December 31, 2018. We analyzed the total sales costs and market share of AODs including bisphosphonates, selective estrogen receptor modulators (SERMs), parathyroid hormone (PTH), calcitonins, and denosumab using the number of days of therapy (DOT). Changes of prescription patterns including original versus generic drugs, vitamin D combination, and types of medical institutions were also analyzed.

**Results:** Bisphosphonates were the most frequently used drug during the study period although its DOT declined from 92.5% in 2008 to 80.0% in 2018. SERMs were the second-most used medication, and has maintained around 13% since 2015. The proportion of calcitonins has decreased since 2011, mainly due to malignancy risk. In contrast, the DOT of PTH and denosumab increased to 0.8% and 4.7% in 2018, respectively. The use of generics, vitamin D combination, and intravenous bisphosphonates has been increasing throughout the study period.

**Conclusions:** Prescription patterns using DOT are changing probably due to the increase in older adult patients and severely osteoporotic patients. There are other issues including safety and the launching of new drugs.

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## 1. Introduction

In 2019, there were 702.9 million people aged 65 years and older worldwide. This number is projected to exceed 1.5 billion people in 2050 [1]. Population aging is an inevitable global trend because of decreasing birth rates due to changes in social structure and people living longer due to advances in public health and medicine [2].

South Korea is a country with a rapidly growing population aged 65 years or over [1]; in 2000, the elderly population accounted for 7.3% of the population and thereafter, Korea became an aging

society. In 2017, the elderly accounted for 14.2% of the population [3]. This figure is expected to reach 20.3% in 2025 and Korea will be considered a super-aged society. It is predicted that South Korea will become the oldest society in the world by 2067, with the elderly accounting for 46.5% of the total population [4].

Age-related chronic diseases are an emerging issue due to increased social costs and loss of labor [5,6]. Osteoporosis, which impairs the bone remodeling process resulting in fragility fractures, is one of the most common chronic diseases in the elderly population [7,8]. According to a fact sheet published by the International Osteoporosis Foundation, 200 million women have osteoporosis worldwide and 8.9 million osteoporotic fractures occur annually, and one in three women and one in five men aged over 50 could experience fragility fractures in their lifetime [9].

Awareness of and adherence to osteoporosis medication are quite low because there are no significant symptoms before an

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individual experiences an osteoporotic fracture [10,11]. The prescription pattern for osteoporosis treatment is changing according to effectiveness, safety, and cost [7,12]. However, there have been no follow-up studies in South Korea since Park published an analysis of sales patterns for anti-osteoporosis medications (AODs) from 2004 to 2008 [12]. Therefore, we analyzed the patterns of sales audit for AODs from the Intercontinental Medical Statistics (IMS) Health in South Korea.

## 2. Methods

AODs are classified into bone resorption inhibitors and bone forming agents. The former consists of bisphosphonates, selective estrogen receptor modulators (SERMs), receptor activator of nuclear factor  $\kappa$ -B ligand inhibitor (denosumab), calcitonins (salmon and eel calcitonin), ipriflavone, vitamin K (menatetrenone), and strontium ranelate. The latter is a parathyroid hormone (PTH; teriparatide). In addition, unclassified drug includes active vitamin D (calcitriol and alfacalcidol) [13]. As of 2018, the Korea Food and Drug Administration (KFDA) has approved bisphosphonates, SERMs, eel calcitonin, denosumab, PTH, active vitamin D for osteoporosis, but had previously approved salmon calcitonin, ipriflavone, menatetrenone, and strontium ranelate.

We obtained the sales audit data for osteoporosis medication from January 2006 to December 2018 through IQVIA (IMS Health Korea). IMS Health data included KFDA-approved bisphosphonates, SERMs, denosumab, and teriparatide. Calcitonins were also included for analysis even though the approval for salmon calcitonin for osteoporosis was withdrawn in September 2013, because they were the third-most used AOD in South Korea until 2016. However, certain bisphosphonates and denosumab approved for cancers were not included for this analysis. Menatetrenone and ipriflavone were excluded because they were used in less than 1% of cases [12,13], and there were not enough data about osteoporosis and fractures [14,15]. Strontium ranelate was also excluded because it was never sold for osteoporosis in South Korea due to concerns of venous thromboembolism (VTE) [16]. Active vitamin D was not included mainly due to prescription with other indications including hypocalcemia, hypoparathyroidism, and chronic renal failure [17,18]. Estrogens were also not included as they are not approved for osteoporosis, and are mainly prescribed for menopausal symptoms [13]. Using IMS Health sales data for South Korea, we analyzed the total sales trend and compared each drug by the number of days of therapy (DOT) which provides a value that is

numerically comparable with AODs use and is less likely to be affected by price differentials and dosing schemes [19].

## 3. Results

The total annual sales have approximately doubled from 98 billion Korean won (KRW) in 2006 to 198 billion KRW in 2018 (Fig. 1). Bisphosphonates, which accounted for an average of 90% from 2006 to 2010, have ranked first in terms of DOT over the past 13 years. However, the number of DOT began to decrease from 2012, and bisphosphonates accounted for 80.0% of total DOT of AODs in 2018. SERMs were the second most used AOD in 2006 at 8.6%. It gradually decreased, reaching the lowest recorded amount of 4.5% in 2011. Since then, the number of DOT have increased and reached 13.9% in 2018. Calcitonins ranked third in the number of DOT of all AODs in 2006 at 2.9%. It had increased up to 7.0% in 2011 and ranked second from 2009 to 2011. But it has steadily declined since 2011 and it was the least used AOD at 0.7% in 2018. In contrast, the number of DOT of PTH has constantly increased from 0.02% to 0.84% for the past 13 years, even with a small percentage. Denosumab rapidly increased from 0.1% to 4.7% with the approval of KFDA in 2016 and expansion of reimbursement policy in 2018 (Table 1). Menatetrenone accounted for less than 1% of all prescribed AODs, and has not been used since 2018 due to withdrawal of the approval from KFDA in 2017. Until 2012, ipriflavone was prescribed in only 0.2% of cases and KFDA approval was withdrawn in 2015 because of safety concerns, such as lymphocytopenia [15].

More than a half of AODs sold by 2012 were original drugs; however, after the expiration of the patent for such drugs, the DOT of generics exceeded an average of 50% since 2013. This pattern is similar to the DOT of bisphosphonates. The original bisphosphonates made up average 62.0% of DOT of all AODs until 2012, but the DOT proportion of generics occupied over 72.4% in 2016–2018. The use of original SERMs has overtaken that of generic SERMs over the study period. As the patent of calcitonins expired in 2000, generics continued to constitute the majority of the market share. PTH and denosumab dominate the market accounting for 100% original drugs (Table 2).

Single agent bisphosphonates are still more widely used, but the number of DOT of bisphosphonates containing vitamin D are slowly increasing (Fig. 2 (a)). According to the administration route of bisphosphonates, oral medications were mainly used, but the proportion of DOT of intravenous agents increased considerably from 2.0% in 2006–2009 to 33.7% in 2016–2018, mainly due to the

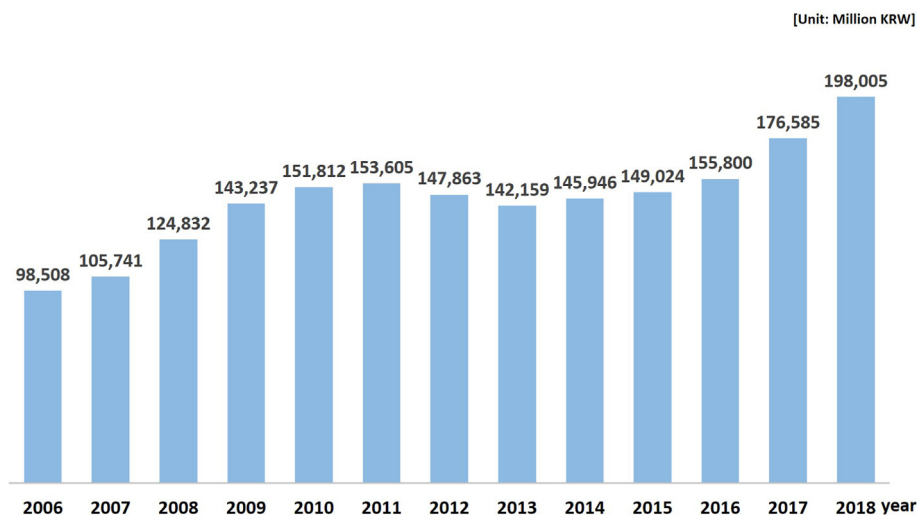


Fig. 1. Annual total sales of anti-osteoporotic drugs (AODs).

**Table 1**  
Annual days of therapy (DOT) of AODs according to the class (Alphabetical order).

Class	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
<b>Bisphosphonates</b>	DOT	72,935,538	86,224,482	108,160,406	132,716,721	145,526,790	160,672,143	170,156,636	182,707,121	180,379,433	207,656,324	224,401,859	226,144,604
	Percentage	88.5%	90.5%	92.5%	89.9%	88.9%	88.3%	88.3%	86.9%	87.9%	85.5%	86.2%	84.3%
Alendronate	DOT	50,169,158	59,870,414	73,354,532	71,415,018	66,926,984	63,716,006	59,471,974	57,904,278	53,318,304	72,917,894	72,427,068	64,008,344
	Percentage	60.9%	62.9%	62.7%	48.4%	40.9%	35.0%	30.4%	27.9%	27.9%	25.3%	30.3%	27.2%
Ibandronate	DOT	-	1,188,510	7,114,110	15,047,970	20,834,220	30,359,430	42,542,010	55,632,390	61,265,160	68,929,530	83,182,830	91,709,280
	Percentage	-	1.2%	6.1%	10.2%	12.7%	16.7%	21.7%	26.8%	29.0%	28.6%	31.2%	32.4%
Riseditronate	DOT	22,766,380	25,081,608	26,892,414	44,948,128	55,886,566	64,386,632	67,532,007	68,527,688	59,909,979	55,780,890	55,413,616	54,003,075
	Percentage	27.6%	26.3%	23.0%	30.4%	34.1%	35.4%	34.5%	33.0%	28.4%	23.1%	20.8%	19.1%
Zoledronate	DOT	-	83,950	799,350	1,305,605	1,879,020	2,210,075	610,645	642,765	5,885,990	10,028,010	13,378,345	16,423,905
	Percentage	-	0.1%	0.7%	0.9%	1.1%	1.2%	0.3%	0.3%	2.8%	4.2%	5.0%	5.8%
<b>Calcitonins</b>	DOT	2,366,030	2,268,667	2,227,411	7,684,387	10,578,030	8,767,158	9,721,743	4,423,206	4,357,526	2,039,133	2,116,191	1,846,908
	Percentage	2.9%	2.4%	1.9%	5.2%	6.5%	4.8%	5.0%	2.1%	2.1%	0.8%	0.8%	0.7%
<b>Denosumab</b>	DOT	-	-	-	-	-	-	-	-	-	145,980	2,911,500	13,170,420
	Percentage	-	-	-	-	-	-	-	-	-	0.1%	1.1%	4.7%
<b>PTH</b>	DOT	-	16,240	39,004	45,640	86,576	187,208	247,772	379,736	620,704	835,807	1,860,250	2,388,561
	Percentage	-	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.2%	0.3%	0.3%	0.7%	0.8%
<b>SERMs</b>	DOT	7,088,088	6,722,268	6,485,780	7,179,508	7,507,010	12,355,038	15,704,016	20,329,418	25,723,796	30,310,682	34,993,888	39,270,814
	Percentage	8.6%	7.1%	5.5%	4.9%	4.6%	6.8%	8.0%	9.8%	12.2%	12.6%	13.1%	13.9%
Total AODs	DOT	82,389,656	95,231,657	116,912,601	147,626,256	163,698,406	181,981,547	195,830,167	207,839,481	211,081,459	240,987,926	266,283,688	282,821,307

DOT, days of therapy; PTH, parathyroid hormone; SERM, selective estrogen receptor modulator; AOD, anti-osteoporotic drug.

approval of intravenous ibandronate (Fig. 2 (b)).

We compared the pattern of DOT of AODs among outpatient clinics, inpatient clinics, and hospitals because health care institutions are classified clinics (< 30 beds) and hospitals (≥ 30 beds) based on government categorization of inpatients bed size in South Korea. Outpatient clinics accounted for the majority of AOD prescriptions over the study period despite decreasing from 91.2% to 68.0%. However, the DOT rates for admitted patients gradually increased from 6.2% to 18.4% in hospitals with 30 or more beds, and from 2.6% to 13.6% in inpatient-clinics with fewer than 30 beds (Fig. 3 (a)). The proportion of DOT of bisphosphonates accounted for the majority in outpatient-clinics and hospitals (≥ 30 beds) throughout the study period. In outpatient-clinics, the proportion of SERMs continued to increase from 6.7% to 19.2%, but the use of bisphosphonates decreased from 93.6% to 80.7% since 2010 (Fig. 3 (b)). In inpatient-clinics, calcitonins were the most frequently used medication at 86.7% and bisphosphonates were used in only 13.2% between 2006 and 2009. Since 2013, bisphosphonates have ranked first in number of DOT among all AODs whereas calcitonins accounted for only 3.4% of use in 2016–2018 (Fig. 3 (c)). Since 2016, the use of denosumab in inpatient-clinics and hospitals has been increasing as an emerging AOD, accounting for 3.6% in inpatient-clinics and 8.4% in hospitals. In hospitals, the percentage of DOT of PTH increased from 0.3% in 2006–2009 to 3.1% in 2016–2018 (Fig. 3 (d)).

**4. Discussion**

Estrogen-based hormone therapy was used in the majority of osteoporosis therapy until potent and convenient medications were developed. Since oral bisphosphonates, alendronate and riseditronate, and SERMs, raloxifene, became commercially available in the 1990s, the use of bisphosphonates and SERMs have increased rapidly among the AODs market in the United States [20]. Based on the IMS Health sales audit from 2004 to 2008 in South Korea, a previous study confirmed the increase in total AODs use and the high dependence of bisphosphonates [12]. This trend has continued since then, and the total sales of AODs doubled from 2006 to 2018. Bisphosphonates are still the most used drugs, although the proportion of DOT among all AODs has decreased since 2012. This trend is partly due to adverse effects of long-term use such as osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF) [21]. SERMs are relatively safe for long-term use and their use has begun to increase again for patients with osteoporosis since 2012 [22]. The DOT of PTH is increasing as the number of people with severe osteoporosis increases. In addition, the DOT of denosumab is rapidly increasing after the insurance reimbursement expanded in South Korea in 2018. However, the DOT of calcitonins decreased mainly due to carcinogenic concerns and cancellation of indications for osteoporosis treatment in 2013 [23].

The proportion of generic drugs is increasing due to the expiration of patents for the original drugs, especially bisphosphonates. New drugs such as PTH and denosumab still occupy the majority market share along with original medication. The price barrier caused by patents on these drugs was overcome by the expansion of insurance reimbursement in South Korea.

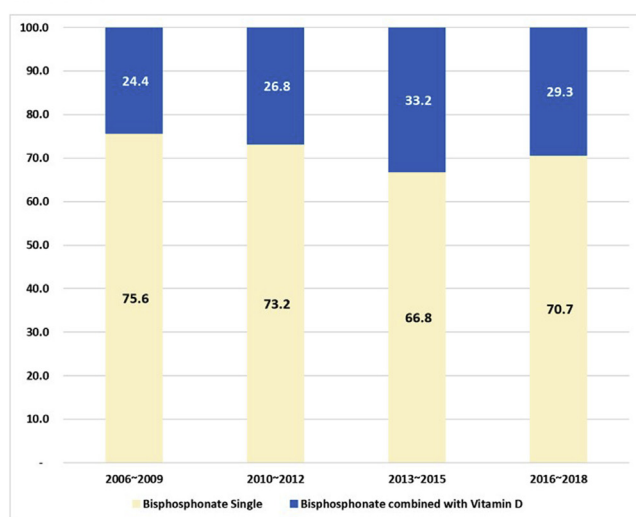
Vitamin D supplementation prior to bisphosphonate therapy can prevent hypocalcemia; furthermore, concurrent vitamin D and bisphosphonate treatment optimize the effectiveness of bisphosphonates [24]. Fixed-combination drug therapy with bisphosphonate and vitamin D is convenient for improving patient compliance to medications because poor adherence for osteoporosis treatment is the primary concern to address [25]. Therefore, increasing the use of bisphosphonates containing vitamin D is a natural trend. To avoid adverse gastrointestinal issues and increase

**Table 2**  
The DOT trends between original and generic AODs (Alphabetical order)

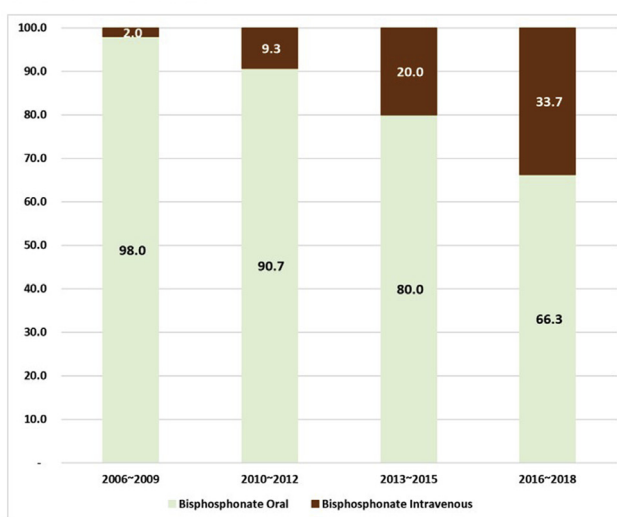
Class		2006–2009	2010–2012	2013–2015	2016–2018
Total AODs	Original drug	66.7	56.6	22.7	35.7
	Generic drug	33.3	43.4	77.3	64.3
Bisphosphonates	Original drug	66.6	58.3	42.8	27.6
	Generic drug	33.4	41.7	57.2	72.4
Calcitonins	Original drug	7.1	1.3	1.0	1.5
	Generic drug	92.9	98.7	99.0	98.5
Denosumab	Original drug	-	-	-	100.0
	Generic drug	-	-	-	-
PTH	Original drug	100.0	100.0	100.0	100.0
	Generic drug	-	-	-	-
SERMs	Original drug	100.0	91.6	94.4	75.8
	Generic drug	-	8.4	5.6	24.2

DOT, days of therapy; AOD, anti-osteoporotic drug; PTH, parathyroid hormone; SERM, selective estrogen receptor modulator.

(a) Formulation



(b) Route of administration



Formulation	2006–2009	2010–2012	2013–2015	2016–2018
Bisphosphonates Single (DOT)	75,643,716	111,047,019	118,821,652	155,177,722
Bisphosphonates combined with Vitamin D (DOT)	24,365,571	40,607,372	58,926,078	64,223,207
Alendronate Single	61.8%	44.2%	32.0%	48.2%
Alendronate combined with Vitamin D	38.2%	55.8%	68.0%	51.8%
Ibandronate Single	100.0%	100.0%	94.7%	89.5%
Ibandronate combined with Vitamin D	0.0%	0.0%	5.3%	10.5%
Risedronate Single	100.0%	91.8%	73.4%	64.5%
Risedronate combined with Vitamin D	0.0%	8.6%	26.6%	35.5%
Zoledronate Single	100.0%	100.0%	100.0%	100.0%
Zoledronate combined with Vitamin D	0.0%	0.0%	0.0%	0.0%

Administration route	2006–2009	2010–2012	2013–2015	2016–2018
Bisphosphonates Oral (DOT)	97,992,698	137,497,796	142,189,970	139,279,212
Bisphosphonates Intravenous (DOT)	2,016,589	14,156,595	35,557,760	70,893,493
Alendronate Oral (DOT)	63,702,281	64,012,591	56,898,185	60,556,211
Alendronate Intravenous (DOT)	-	-	-	-
Ibandronate Oral (DOT)	4,368,285	13,530,030	19,968,560	23,657,140
Ibandronate Intravenous (DOT)	1,469,363	12,223,920	33,177,960	57,616,740
Risedronate Oral (DOT)	29,922,133	59,955,175	65,323,225	55,065,860
Risedronate Intravenous (DOT)	-	-	-	-
Zoledronate Oral (DOT)	-	-	-	-
Zoledronate Intravenous (DOT)	547,226	1,932,675	2,379,800	13,276,753

**Fig. 2.** The days of therapy comparison of bisphosphonates by formulation and route of administration.

patient compliance, intravenous bisphosphonates use continues to increase over the entire analysis period, which is similar to the results of the study by Wysowski et al in the United States [26].

The rapidly growing elderly population is associated with increasing hospitalization for severe osteoporosis [27]. Thus, in contrast to the decrease in AODs use in outpatient-clinics, the use of AODs in inpatient-clinics and hospitals has been increased. Bisphosphonates use accounted for a significant proportion in all medical institutions. In outpatient-clinics, SERMs were the second-most prescribed drug, probably because most of patients are diagnosed as relatively mild osteoporosis with mainly vertebral osteoporosis or osteopenia. In hospitals ( $\geq 30$  beds), as they significantly consist of patients with more severe osteoporosis, PTH and denosumab use increased. Interestingly, in the past, calcitonins were the most frequently used drug in inpatient-clinics ( $< 30$  beds), and its use has decreased since 2013 due to safety concerns and withdrawal of indications for osteoporosis treatment. After

denosumab was released in South Korea in 2016 and its insurance reimbursement was expanded in 2018, the DOT of denosumab is on the rise.

This study has some limitations. First, we estimated the use of AODs only as the number of DOT of drugs sold in the market, so there is a discrepancy as compared to actual drug use and adherence in the real world. Second, some AODs can be overestimated because some are used to treat diseases other than osteoporosis. Nevertheless, we believe that the main AODs used in South Korea are included and there is no difficulty in roughly grasping the overall trends of osteoporosis treatment.

**5. Conclusions**

In South Korea, this analysis confirmed that bisphosphonates are still the predominantly used AODs, even for patients with poor adherence to oral drugs, due to extended interval dosing and

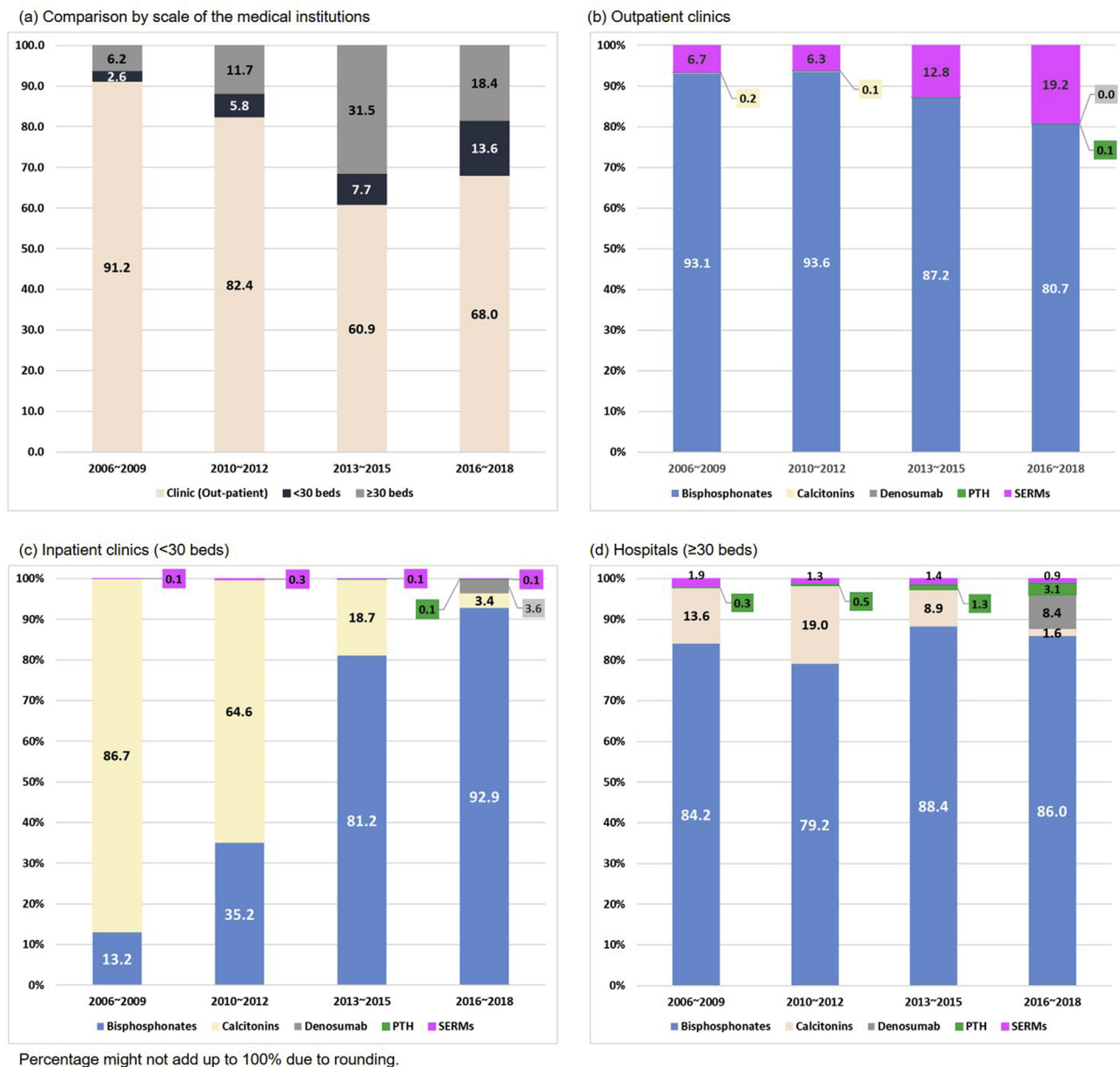


Fig. 3. Differences in days of therapies by the type of medical institution (Alphabetical order).

availability as intravenous injections. However, the use of PTH is increasing as the advanced aging society progresses. The prescription patterns of AODs seem to be changing due to adverse effects such as ONJ and AFF according to the long-term bisphosphonate therapy and the release of new drugs such as denosumab.

**CRedit author statement**

**Nami Lee:** Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Yong Jun Choi:** Methodology, Software, Validation. **Yoon-Sok Chung:** Conceptualization, Writing - review & editing, Supervision.

**Conflicts of interest**

The authors declare no competing interests.

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