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MINI ABSTRACT

Calcium use was common and remained high among women on osteoporosis therapy. Use of calcium-supplemented pharmacologic therapy increased from 65.1% to 76.0% in these women (mean follow-up: 27.5 months). Over 12 months, calcium discontinuation was fairly similar among women using calcium only (23.7%) and women supplementing pharmacologic therapy with calcium (22.5%).

ABSTRACT

Purpose Calcium has an important role in bone health. This study describes calcium use and persistence in a postmenopausal osteoporosis treatment cohort.

Methods Subject-reported calcium use was analyzed for 3,722 participants of the Prospective Observational Scientific Study Investigating Bone Loss Experience (POSSIBLE US™) who used calcium either as their sole osteoporosis treatment (calcium only) or to supplement pharmacologic osteoporosis therapy (supplementers). Descriptive analyses were conducted. Kaplan-Meier methods were used to estimate the probability of discontinuing with calcium therapy, and logistic regression was used to assess associations (age-adjusted odds ratios) between healthy behaviors and calcium use.

Results At entry, there were 711 calcium-only subjects and 1,960 of 3,011 subjects on pharmacologic osteoporosis therapy also supplementing with calcium (supplementers). The percentage of supplementers increased from 65.1% to 76.0% during follow-up (mean: 27.5 months). During the first 12 months on study, the probability of calcium discontinuation was 23.7% (95% confidence interval [CI], 20.7–27.0) among calcium-only subjects and 22.5% (95% CI, 20.7–24.5) among supplementers. Supplementers who discontinued pharmacologic therapy were more likely to discontinue calcium than supplementers who continued pharmacologic therapy (34.9% versus 14.8%). Overall 54.2% of calcium-only subjects who discontinued calcium and 42.3% of supplementers who discontinued calcium resumed calcium use during follow-up. Regular exercise was positively correlated with calcium use at study entry.

Conclusions Calcium supplementation in pharmacologically treated subjects increased over time. Persistence with calcium was high. Discontinuation of pharmacologic osteoporosis therapy was associated with an increased likelihood of discontinuing calcium use.

Keywords Calcium – Discontinuation – Persistence – Postmenopausal osteoporosis

Introduction

Calcium has a key role in the continuous cycle of resorption and reformation that occurs naturally in human bone. In postmenopausal women, resorption typically outpaces bone formation, in part because lower estrogen levels increase the breakdown of bone while simultaneously decreasing the absorption of calcium [1-3]. This imbalance between the two components of the bone remodeling process impacts both bone mineral density and bone quality, and increases the risk of osteopenia, osteoporosis, and fragility fracture.

The National Health and Nutrition Examination Survey (NHANES) has estimated total calcium intake, based on dietary sources and use of calcium supplements, in various demographic groups in the United States (US) [4]. These data, collected through household interviews, provide information on dietary behaviors and supplement use during the previous 30 days. In addition, a 24-hour recall questionnaire is administered to collect subject-reported dietary intake and use of supplements [5, 6]. While this approach provides the data necessary to compute point estimates of total calcium intake and the prevalence of calcium supplementation that can be projected to the national population, the cross-sectional design of NHANES precludes evaluation of persistence with calcium supplements over time.

Despite the known bone benefits of adequate calcium intake and the known physiological changes that predispose postmenopausal women to inadequate serum calcium levels, relatively little is known about the use of calcium supplements among women treated for osteoporosis. The current study sought to describe calcium use as either the sole postmenopausal osteoporosis therapy (calcium only) or in conjunction with a pharmacologic osteoporosis agent (supplementers) in the Prospective Observational Scientific Study Investigating Bone Loss Experience (POSSIBLE US™) osteoporosis treatment cohort.

Methods

Data source and study population

From October 2005 to January 2007, 5,015 postmenopausal women who were receiving calcium and/or pharmacologic osteoporosis therapy for bone loss were enrolled into the POSSIBLE US™ by 134 primary care physicians across the US. All subjects provided informed consent in this Institutional Review Board approved longitudinal cohort study. At a routine visit with the primary care physician, each subject received prescriptions or recommendations for one or more of the following osteoporosis treatments as part of their usual medical care: oral bisphosphonate (alendronate/alendronate sodium with cholecalciferol, risedronate/risedronate with calcium, ibandronate), oral or transdermal postmenopausal estrogen (PME), teriparatide (rhPTH(1-34)), calcitonin, raloxifene, or calcium with or without vitamin D.

At the routine visit, each subject completed a written self-administered baseline questionnaire to report demographic characteristics and lifestyle behaviors, osteoporosis medication use, treatment satisfaction (Treatment Satisfaction Questionnaire for Medications [7] [TSQM, Quintiles, Inc., Research Triangle Park, NC, USA]) and treatment-related side effects, and health-related quality of life (EuroQolEQ-5D™ [8] [EuroQol Group, Rotterdam, The Netherlands]). Follow-up questionnaires, mailed to subjects every 6 months after study entry for up to 3 years, collected the same information and also asked about the occurrence of on-study fractures. Physicians provided relevant medical history for each enrolled subject at study entry, with updates provided from routine visits during the follow-up period. Additional details of the POSSIBLE US™ study design, subject recruitment, and data collection have been reported previously [9]. This study included all subjects who had completed at least one follow-up questionnaire.

Self-reported use of calcium and pharmacologic osteoporosis therapy

On each questionnaire, subjects were instructed to complete a separate medication use page for each osteoporosis medication used during the previous 6 months. Each medication page provided 12 tick boxes (one for each month of the year) and subjects were asked to mark all months during the last 6 months in which they used a specified osteoporosis medication. Subjects used specific medication codes for each approved pharmacologic osteoporosis therapy marketed during the study period. Since calcium use was also of interest, a separate medication code was provided for reporting use of the risedronate formulation that includes calcium. The data collection forms also provided a code for reporting calcium with or without vitamin D. This wording did not allow us to isolate vitamin D supplementation in the study cohort; thus, for simplicity, we use the term “calcium” to report these results.

The monthly medication use data were analyzed to identify discontinuations of calcium and pharmacologic osteoporosis therapy. Discontinuation was defined as the reported nonuse of the baseline osteoporosis medication (ie, calcium or pharmacologic osteoporosis therapy) for 3 or more continuous months with the discontinuation date set to the first month in this period of nonuse. These definitions were also used previously to assess medication persistence in the POSSIBLE US™ cohort [10]. Here we use the term discontinuation to encompass discontinuations that were part of medication switches.

The primary analyses reported are based on the data obtained from the subset of subjects from the POSSIBLE US™ cohort who at or shortly after study entry reported either using calcium alone or using calcium to supplement a pharmacologic osteoporosis therapy. An additional analysis reports the initiation of calcium use in subjects who were using only prescription pharmacologic osteoporosis therapy at study entry.

Statistical analysis

For reporting purposes, subjects were classified into the following three groups using self-reported medication use: subjects who reported using calcium as their sole osteoporosis therapy at or within 2 months of study entry (calcium only); subjects who reported supplementing pharmacologic osteoporosis therapy with calcium or using a pharmacologic osteoporosis therapy that included calcium as part of the formulation at or within 2 months of study entry (supplementers); subjects who reported using only pharmacologic osteoporosis therapy at or within 2 months of study entry (pharmacologic only). This approach provided subjects a maximum of 2 months in which to initiate any osteoporosis therapies prescribed at the study enrollment visit.

Descriptive statistics were assessed for key demographic and clinical characteristics at study entry. Characteristics were compared between subjects in the calcium-only group and subjects who used a pharmacologic osteoporosis agent with or without calcium supplementation (combined population), using t-tests for continuous data and chi-square tests for categorical data.

We examined utilization patterns for subject-reported calcium use among calcium-only subjects and supplementers. Kaplan-Meier methods were used to estimate the probability of persisting with calcium during the first 12 months after study entry. For these analyses, subjects with no evidence of a medication discontinuation or switch were censored at the date of therapy augmentation (addition of another agent to the index regimen described above), loss to follow-up, death, or end of the observation period, whichever came first.

Persistence with calcium was assessed separately for calcium-only subjects and supplementers. Among supplementers, subjects who discontinued pharmacologic osteoporosis

therapy in the first year on study were identified, and then the percentage of subjects who continued using calcium after discontinuing their pharmacologic osteoporosis therapy was determined. For all subjects who discontinued calcium use in the first year on study, all available follow-up data were used to determine whether they resumed calcium use later in follow-up. Restart results are presented separately for calcium-only subjects and for supplementers. In this latter group, the percentage of subjects who re-initiated calcium therapy after discontinuing both calcium use and pharmacologic osteoporosis therapy was determined.

Finally, a multivariate model was constructed to examine associations between calcium use and the three markers of healthy behavior for which data were obtained at study entry: subject reported not smoking, healthy body mass index (BMI; 18.5–24.9 kg/m²) based on physician-reported weight and height, and subject-reported regular physical activity/exercise. This model estimated unadjusted and age-adjusted odds ratios and 95% confidence intervals (CIs) for each of these three health behaviors.

Initial analyses of the distributions of key variables suggested a high level of data completeness, and, therefore, missing data were not imputed. All statistical analyses were conducted using SAS[®] version 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results

Data were analyzed for 3,722 subjects from the POSSIBLE US[™] cohort who reported osteoporosis monotherapy at or within 2 months of study entry (Fig. 1). At study entry, 711 of these subjects reported using calcium as their sole osteoporosis therapy (calcium only) and 3,011 subjects reported using pharmacologic osteoporosis therapy, of whom 1,960 (65.1%) reported also using calcium at study entry (supplementers) and the remainder (1,051) used only pharmacologic agents (pharmacologic only). Compared with subjects using pharmacologic

osteoporosis therapy ($n=3,011$), calcium-only subjects were younger, more likely to be overweight or obese, more likely to have either no osteoporosis diagnosis or a physician-reported diagnosis of osteopenia (all $p<0.0001$), and less likely to have had a prior fragility fracture (i.e., fracture after age 50, $p=0.004$) (Table 1). The specialty distribution of enrolling physicians also differed between subjects using calcium only and those using pharmacologic osteoporosis therapy ($p<0.0001$) (Table 1). Mean (SD) follow-up was 27.5 (10) months.

The percentage of supplementers increased to 76.0% (2,287/3,011) over the follow-up period as pharmacologic therapy users added calcium to their treatment regimens. Supplementers reported concurrent calcium use in 83.6% of the months that pharmacologic osteoporosis therapy was used (83.3% for subjects using bisphosphonate therapy, 84.8% for subjects using non-bisphosphonate therapy). However, concurrent use of calcium and pharmacologic therapy only occurred in 64.1% of all follow-up months due to discontinuations of pharmacologic therapy, calcium supplementation, or both.

Over 12 months of follow-up, calcium discontinuation was fairly similar among calcium-only subjects and supplementers. Overall, 76.7% calcium-only subjects and 75.2% supplementers continued using calcium during this period (Table 2). Among supplementers who discontinued the pharmacologic osteoporosis therapy used at study entry ($n=981$), 34.9% also stopped using calcium. By contrast, only 14.8% of supplementers who continued pharmacologic osteoporosis therapy discontinued calcium. The population attributable risk (34.9% minus 14.8%) indicates that the supplementers who discontinued their pharmacologic osteoporosis therapy had a 20% greater likelihood of also discontinuing calcium. The proportion of supplementers who discontinued both the pharmacologic osteoporosis agent reported at study entry and calcium was 34.0% among subjects who used bisphosphonates and 36.9% among those who used other pharmacologic osteoporosis therapies.

Since the duration of follow-up varied in the study population, Kaplan-Meier methods were used to estimate the probability of discontinuing calcium use during the first 12 months on study. Based on evaluation of 8,232 subject-months, calcium-only subjects had a 23.7% (95% CI: 20.7–27.0) probability of discontinuing calcium. Supplementers (22,464 subject-months) had a similar (22.5%; 95% CI: 20.7–24.5) probability of discontinuing calcium. Among subjects who stopped using calcium for at least 3 months, 54.2% (90/166) of the calcium-only subjects and 42.3% (206/487) of the supplementers resumed calcium use before the end of follow-up.

Among the subjects who used pharmacologic osteoporosis therapy only (i.e., no calcium use) at entry, 46.5% (489/1,051) discontinued the pharmacologic osteoporosis therapy reported at study entry, and of those subjects, 26.4% (129/489) later began using calcium.

Based on age-adjusted odds ratios and 95% CIs, self-reported regular exercise was the only one of the three healthy behaviors examined (i.e., not smoking, healthy BMI, exercise) that was positively associated with calcium use at study entry (Table 3). The age-adjusted point estimate suggested that subjects who reported not smoking were also more likely to have used calcium, but this difference was not statistically significant.

Discussion

A variety of effective therapies with different modes of administration and mechanisms of action are available for both the prevention and treatment of osteoporosis [11]. In addition to pharmacologic osteoporosis therapy, research suggests that calcium supplementation (with or without vitamin D) has an important role in management of osteoporosis since inadequate calcium intake increases the risk of osteopenia and osteoporosis [12]. Overall in our study

population, 71.8% (2,671/3,722) of subjects reported calcium use at study entry, either as their sole osteoporosis therapy ($n=711$) or as supplemental to pharmacologic therapy ($n=1,960$).

Treatment guidelines and product packaging for pharmacologic osteoporosis medications often recommend that calcium and vitamin D supplements be used in conjunction with the pharmacologic osteoporosis agent [13]. This recommendation is based on the fact that osteoporosis clinical trials have generally been conducted in subjects who were receiving adequate levels of calcium and vitamin D, and in general, women with osteoporosis have an increased risk of presenting with calcium and/or vitamin D deficits [14, 15]. In the POSSIBLE US™ cohort, a considerable proportion of pharmacologically-treated subjects were not using calcium during their time on study. However, it was encouraging to see that the percentage of pharmacologically-treated subjects supplementing with calcium increased from 65.1% to 76.0% during follow-up.

Studies report that the frequency with which calcium supplements are co-prescribed for subjects receiving pharmacologic osteoporosis treatment varies [14, 16]. Surveys of primary care physicians in the US who participated in the National Osteoporosis Risk Assessment (NORA) study indicated that calcium supplementation was recommended to 87% of postmenopausal subjects (age 50 and older) in 1998 and to 90% of subjects in 2006 ($p=0.0006$) [16]. By contrast, in a study of postmenopausal women in France who initiated osteoporosis treatment between May and August 2010, 51% received a co-prescription for calcium (with or without vitamin D) [14]. An additional 26% of these women were co-prescribed vitamin D only.

The probability of persisting on calcium therapy during the first 12 months on study was over 75% both in subjects who were using calcium only and in supplementers. This is considerably higher than the persistence rates reported in the literature for pharmacologic osteoporosis

therapies [10, 17], including the 66% (95% CI: 64%–68%) 12-month probability of persistence with pharmacologic osteoporosis therapies previously reported for the POSSIBLE US™ cohort [10].

Few studies have reported persistence with calcium only. An Italian study reported that among 1,680 postmenopausal women treated with calcium (with/without vitamin D), 14.3% discontinued within 6 months, an additional 5.4% discontinued between 6 and 12 months, and 2.9% discontinued after 12 months (median follow-up: 14 months) [18]. A multicenter cross-sectional study in Spain examined persistence in subjects age 45 years and older who had received a prescription for calcium plus vitamin D at least 1 year earlier [19]. Among these subjects, women using calcium for a variety of conditions including osteoporosis, 27.7% had discontinued by the time the cross-sectional study was completed.

In the present study, supplementers who stopped using the pharmacologic osteoporosis therapy reported at study entry were less likely to continue using calcium compared with subjects who persisted on the pharmacologic osteoporosis therapy reported at entry (85.2% versus 65.1%). This finding suggests that whatever factors may predispose a patient to discontinue prescription osteoporosis therapy may also influence persistence with calcium therapy, although we were not able to explicitly test this hypothesis because data on reasons for discontinuation were not adequately captured. On the other hand, over one-quarter of the subjects who discontinued a pharmacologic-only regimen initiated calcium use later during follow-up, which suggests an interest in pursuing osteoporosis treatment in some form.

Data from NHANES III (2003–2006) indicate that more than half of women over age 70 and women age 51 to 70 years have dietary calcium intakes below the then recommended levels for their respective age and sex groups [4]. In NHANES III, 67% of women age 51 to 70 and 65%

of women age 70 and older reported using calcium supplements, with these supplements providing an average of 578 mg/day and 608 mg/day, respectively. Even with these supplements, only an estimated 39% of women older than age 50 achieved the recommended calcium intake. Despite these disappointing results, the use of calcium supplements by women age 60 and older has increased over time: 28.2% (1988–1994), 53.8% (NHANES, 1999–2002), and 61.0% (NHANES, 2003–2006) [20].

In the POSSIBLE US™ cohort, 72% of women used calcium, which is higher than the 64% reported for osteoporosis subjects with earlier data in NHANES from 1999–2002 [21]. This difference may reflect the specific recruitment of calcium users into POSSIBLE US™, or the overall increased use of calcium supplements over time reported by older women who participated in NHANES.

Regular exercise was the only health behavior evaluated that was correlated with calcium use in our study cohort. This finding is important since other research suggests that physical activity and calcium intake may have synergistic bone benefits. A Greek study, for instance, posits a complementary effect on bone mass for regular physical activity and adequate calcium intake, with increased bone stiffness in the active post- and premenopausal women compared with their sedentary counterparts [22].

Despite general agreement that calcium is important to bone health, current clinical recommendations are still mixed. The Institute of Medicine recently conducted an assessment of data on calcium (reported in 2008) and concluded that calcium provided significant bone benefits, especially for postmenopausal women [23]. Results from a large-scale calcium/vitamin D supplementation trial conducted within the Women's Health Initiative (WHI) demonstrated that supplementation had the potential to increase bone mineral density and to reduce hip fracture

risk among women who were adherent to therapy and who had been taking supplements for 5 years or longer [24]. The Agency for Healthcare Research and Quality's comparative effectiveness review of osteoporosis therapies reported that the evidence demonstrating reductions in nonvertebral fracture with calcium monotherapy was moderately strong, with strong evidence for the role of calcium therapy in reducing hip fracture risk [25].

By contrast, in 2013, the US Preventive Services Task Force recommended against supplementation with $\leq 1,000$ mg of calcium and ≤ 400 IU of vitamin D₃ for postmenopausal women, and also noted that the evidence regarding higher dose levels was inadequate to make a recommendation for or against supplementation [13]. In particular, although a 12% reduction in hip fracture rate observed for the postmenopausal women (age 50 to 79 years) in the WHI cohort who were supplementing with 1,000 mg of calcium daily was statistically significant, the US Preventive Services Task Force did not consider this effect large enough to recommend calcium supplementation at this level for primary prevention of fractures in postmenopausal women. This recommendation was given despite the statistically significant 21% reduction in hip fracture rate that was reported among calcium supplementers in the WHI cohort who were age 60 and older, and the statistically significant 30% reduction in hip fracture rate among women who were compliant with calcium supplementation [26].

Risk benefit is a consideration in decisions to prescribe calcium supplementation for osteoporosis patients, and several studies have examined the safety of calcium supplementation, in terms of the risk of cardiovascular disease (CVD) or events [27-34]. Results of those studies have been mixed. Some studies [27-31, 34], including an analysis of data collected in the Women's Health Initiative (WHI) randomized controlled trial [29] and a meta-analysis of 15 randomized controlled trials including the WHI [27], have reported associations between calcium supplementation and increased risk of CVD and related events,

such as CVD-related deaths in men only, [34] and myocardial infarction. By contrast, a recent analysis of NHANES III data examining the safety of calcium supplementation found no association between dietary or supplementary calcium intake and risk of CVD-related death [35]. Furthermore, when the WHI trial data were combined with data from over 93,000 postmenopausal women who had approximately 8 years of follow-up in the WHI observational cohort study, calcium supplementation had no apparent effect on the risk of CVD or CVD-related events (e.g., myocardial infarction, stroke) [32].

Results from our study should be interpreted within the limitations of this study. First, the POSSIBLE US™ cohort includes only postmenopausal women who were treated for bone loss by their primary care physician and were receiving osteoporosis medications. The women in this cohort represent a selected population of women identified for osteoporosis treatment and who were willing to participate in an observational study. These women may differ demographically and clinically from postmenopausal women in general, and may also exhibit different health-related behaviors. Although the original POSSIBLE US™ paper concluded that the women in this cohort are demographically similar to women treated for osteoporosis in the US, they may not be representative of women with postmenopausal bone loss overall or of women treated for bone loss in other countries where osteoporosis treatment guidelines and product labeling may differ. Secondly, since very large calcium supplements are now provided over-the-counter, studies of calcium use must rely on patient self-report. Our reliance on subject-reported medication use for this study may result in overestimation of the proportion of subjects using and/or persisting on calcium therapy.

In summary, utilization of and persistence with calcium was high in this cohort of postmenopausal women who were receiving osteoporosis therapy. Discontinuation of pharmacologic osteoporosis therapy was associated with an increased likelihood of

discontinuing calcium use. A number of subjects who entered the study on a pharmacologic osteoporosis agent appeared to have switched to calcium only during follow-up. In addition, the proportion of women who used calcium to supplement pharmacologic osteoporosis therapy increased during follow-up.

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Conflict of interest

Funding for this study was provided by Amgen Inc.

EBC, RWD, TG, MH, and RRR previously received remuneration from Amgen Inc. for participation in the POSSIBLE US™ Steering Committee.

SWW has received consulting fees from Amgen Inc.

BS is an employee of Amgen Inc. and own Amgen Inc stock and/or stock options.

Statement of Human Rights

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration. Informed consent was obtained from all participants in the study.

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Figure legend

Fig. 1 Subject Selection

Table 1. Characteristics of subjects at study entry by type of osteoporosis therapy used^a

	Calcium only	Pharmacologic therapy ^b
Total number of subjects	711	3,011
Age, mean (SD), years*	61.2 (9.0)	64.6 (9.7)
Age range, min, max, years	40, 91	37, 97
Age group*		
< 45 years	6 (0.8)	17 (0.6)
45–54 years	174 (24.5)	472 (15.7)
55–64 years	302 (42.5)	1,070 (35.5)
65–69 years	91 (12.8)	490 (16.3)
70–74 years	73 (10.3)	409 (13.6)
≥ 75 years	65 (9.1)	553 (18.4)
Race/ethnicity		
Caucasian/White	648 (91.1)	2,728 (90.6)
African-American	23 (3.2)	86 (2.9)
Asian	7 (1.0)	32 (1.1)
Hispanic/Latino	21 (3.0)	101 (3.4)
Other	12 (1.7)	64 (2.1)
Education		
High school or less	269 (37.8)	1,206 (40.1)
At least some college	442 (62.2)	1,805 (60.0)
BMI*		
< 18.5 (underweight)	21 (3.0)	85 (2.8)
18.5–22.6 (normal)	88 (12.4)	658 (21.9)
22.7–24.9 (normal)	109 (15.3)	631 (21.0)
25.0–29.9 (overweight)	243 (34.2)	977 (32.5)
≥ 30.0 (obese)	250 (35.2)	660 (21.9)
Bone loss diagnosis at study entry*		
Osteoporosis	85 (12.0)	1,322 (43.9)
Osteopenia	373 (52.5)	1,502 (49.9)
Other	13 (1.8)	14 (0.5)
None	240 (33.8)	173 (5.8)
Minimum T-score (hip/spine) at diagnosis*		
Number of patients with score	491	2,649
T-score ≥ –1	110 (22.4)	206 (7.8)
–2 < T-score ≤ –1	270 (55.0)	934 (35.3)
–2.5 < T-score ≤ –2	57 (11.6)	576 (21.7)

	Calcium only	Pharmacologic therapy ^b
-3 < T-score ≤ -2.5	26 (5.3)	473 (17.9)
T-score ≤ -3	28 (5.7)	460 (17.4)
History of fracture since age 50*	111 (15.6)	615 (20.4)
Parental history of hip fracture	33 (4.6)	168 (5.6)
On-study fracture*	63 (8.9)	355 (11.8)
Before age 60	31 (4.4)	108 (3.6)
On or after age 60*	31 (4.4)	237 (7.9)
Glucocorticoid steroid use in 6 months prior to study entry	9 (1.3)	55 (1.8)
Rheumatoid arthritis	50 (7.0)	206 (6.8)
Current smoker	73 (10.3)	270 (9.0)
No regular exercise	138 (19.4)	583 (19.4)
Number of comorbidities per subject, mean (SD)	2.7 (2.1)	2.7 (2.3)
Specialty of enrolling physician*		
Internal medicine	303 (42.6)	1,024 (34.0)
OB/GYN	210 (29.5)	988 (32.8)
Family medicine	187 (26.3)	972 (32.3)
Other	11 (1.6)	27 (0.9)

^aBased on subject-reported medication use at or within 2 months of study entry.

^bWith or without calcium supplementation.

*Significant differences between calcium only and pharmacologic therapy patients, $p < 0.005$. Values are n (%) unless otherwise noted.

Table 2. Discontinuation of calcium use during first 12 months on study

	Total number of subjects <i>n</i>	Subjects discontinued calcium therapy in first 12 months on study <i>n</i> (%)	Subjects continued calcium therapy throughout first 12 months on study <i>n</i> (%)
Subjects using calcium only ^a	711	166 (23.4)	545 (76.7)
Subjects supplementing pharmacologic osteoporosis therapy with calcium (supplementers) ^a	1960	487 (24.9)	1473 (75.2)
Subjects who continued pharmacologic therapy throughout first 12 months on study	979	145 (14.8)	834 (85.2)
Bisphosphonate users ^a	700	103 (14.7)	597 (85.3)
Non-bisphosphonate users ^a	279	42 (15.1)	237 (85.0)
Subjects who discontinued pharmacologic therapy in first 12 months on study ^b	981	342 (34.9)	639 (65.1)
Bisphosphonate users ^a	683	232 (34.0)	451 (66.0)
Non-bisphosphonate users ^a	298	110 (36.9)	188 (63.1)

^aBased on subject-reported medication use at or within 2 months of study entry.

^bDiscontinuation was marked by at least 3 months of patient-reported non-use of osteoporosis medication.

Table 3. Associations between healthy behaviors and calcium use at study entry

Healthy characteristics/behaviors at study entry ^a	Unadjusted odds ratio	95% confidence interval	Age-adjusted odds ratio ^b	95% confidence interval
Not smoking	1.08	(0.85–1.38)	1.12	(0.88–1.43)
Normal BMI (18.5–24.9 kg/m ²)	0.93	(0.77–1.12)	0.94	(0.78–1.13)
Regular exercise	1.42	(1.19–1.70)	1.38	(1.15–1.65)

^aNumber of subjects with non-missing responses:

Current smoking: Yes: 343 subjects, No: 3,352 subjects

Normal BMI: Yes: 1,486 subjects, No: 2,236 subjects

Regular exercise: Yes: 3,001 subjects, No: 721 subjects

^bAdjusted for patient age at study entry.

Fig. 1 Subject Selection