Background: Although many studies have assessed the effects of estrogen and raloxifene hydrochloride on bone mineral density and serum lipid concentrations, there are few direct comparative data.

Methods: Randomized placebo-controlled trial for 3 years, intention-to-treat analysis. Six hundred nineteen postmenopausal women with prior hysterectomy (mean age, 53.0 years) were studied in 38 centers in Europe, North America, Australasia, and South Africa. They were randomized to 60 mg/d or 150 mg/d of raloxifene, 0.625 mg/d of conjugated equine estrogen (CEE), or placebo. Bone density of the lumbar spine and proximal femur, biochemical markers of bone turnover, and fasting serum lipid concentrations were assessed for 3 years.

Results: Compared with baseline, bone density in the lumbar spine progressively declined by 2.0% in the placebo group ($P<.05$), was stable in the 2 raloxifene groups, and increased 4.6% in the subjects receiving CEE ($P<.001$). Effects in both raloxifene groups were different from those observed in the CEE and placebo groups ($P<.001$). Bone density in the total hip showed similar results. Conjugated equine estrogen produced significantly greater depression of serum osteocalcin, bone-specific alkaline phosphatase, and urine C-telopeptide, compared with raloxifene. Each of the active treatments caused comparable depression of low-density lipoprotein cholesterol below placebo levels ($P<.001$ at most time points). Raloxifene did not affect high-density lipoprotein cholesterol, whereas CEE increased it by 13.4% compared with placebo at 3 years ($P<.001$). Triglyceride concentrations increased 24.6% in the CEE group at 3 years ($P<.003$), a significantly greater change than in the raloxifene groups, which were 4.9% and 8.0% above baseline ($P<.002$) but not different from placebo. Urinary incontinence was reported in 11 women receiving CEE, but in only 1 or 2 in each of the other groups ($P<.01$ compared with the other groups). Hernias occurred less frequently in those receiving 150 mg/d of raloxifene or CEE ($P=.03$ vs placebo).

Conclusions: Raloxifene and CEE have beneficial effects on bone density and bone turnover, although effects of CEE are more marked. Raloxifene and CEE produce different patterns of lipid responses and have distinct adverse effect profiles.

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however, antiproliferative effects of raloxifene in reproductive tissues have been demonstrated. Long-term raloxifene treatment leads to no increase in uterine bleeding or mastalgia and to greater than 70% reduction in risk for invasive breast cancer in subjects with osteoporosis followed up for 4 years.²⁰

The recent premature termination of the estrogen-progestin arm of the Women’s Health Initiative¹⁰ has placed a renewed emphasis on alternatives to conventional hormone therapy in the management of osteoporosis and cardiovascular disease. Although short-term direct comparisons of the effects of raloxifene and estrogen therapy on lipid metabolism have been reported,⁷ long-term comparative data are not available for the lipid or skeletal effects of these agents. The present study has addressed this issue in a randomized controlled trial of 3 years’ duration. Because it is difficult to conduct long-term blinded trials of estrogen therapy in normal postmenopausal women, as uterine changes are likely to result in unblinding, the present study was restricted to women who had previously undergone a hysterectomy.

STUDY POPULATION

Women were eligible to participate if they were 40 to 60 years of age, postmenopausal (naturally or surgically), had undergone a hysterectomy no more than 15 years before beginning the study, had serum estradiol levels of 20 pg/mL (<73 pmol/L) and follicle-stimulating hormone levels of 40 mIU/mL or higher, and had a lumbar spine BMD measurement between 2.5 SDs below and 2.0 SDs above the mean value for normal premenopausal women. Women were excluded from the study if they had a history of carcinoma of the breast or estrogen-dependent tumors; had cancer within the last 5 years (except excised skin cancers); had taken estrogen (other than vaginal estrogens), progestin, androgen, calcitonin, or systemic corticosteroids within the previous 6 months; had ever taken bisphosphonate or fluoride (except for dental prophylaxis); were taking antiseizure medications; were taking pharmacologic dosages of vitamin D or lipid-lowering drugs; had a history of thromboembolic disorders or of diabetes mellitus or other endocrine disorders requiring therapy (except thyroid hormone therapy); had abnormal renal function or hepatic function; had serious postmenopausal symptoms; or consumed more than 4 alcoholic drinks per day. The protocol was approved by the human studies review board at each center. All women gave written informed consent to their participation in the study in accordance with the ethical principles stated in the Declaration of Helsinki.

STUDY DESIGN

This phase 3 double-blind randomized placebo-controlled trial was conducted at 38 sites in Europe, North America, Australasia, and South Africa. Women were assigned to 1 of 4 therapy groups, on the basis of a randomized block design (block size, 4): 60 mg/d of raloxifene, 150 mg/d of raloxifene, 0.625 mg/d of conjugated equine estrogen (CEE) (Premarin; Wyeth-Ayerst, Madison, NJ), or placebo. All the women were also given a daily supplement of 400 to 600 mg of elemental calcium. Study visits occurred every 3 months for 24 months and then every 6 months through 36 months. Serum lipids and biochemical markers of bone turnover were measured at every visit. Bone mineral density of the spine and hip was determined every 6 months until 24 months, then at end point. The women were questioned at each visit about the occurrence and severity of adverse events.

ANALYTIC PROCEDURES

Bone mineral density of the spine (L1-L4) and total hip was measured by dual-energy x-ray absorptiometry using Hologic (Waltham, Mass) instruments. Scans were reviewed in a blinded fashion at a central facility, which provided correction factors to adjust for changes in the performance of the densitometers over time, as well as cross-calibration between sites. Biochemical markers of bone turnover, including serum osteocalcin (ELSA-OSTEO IRMA; CIS BioInternational, Gif-sur-Yvette, France), serum total and bone-specific alkaline phosphatase (Ostease IRMA; Hybritech, San Diego, Calif), and urinary type I collagen fragment C-telopeptide (CrossLaps ELISA; Osteometer Biotech A/S, Herlev, Denmark) were measured at 2 central laboratories (Covance, Indianapolis, Ind). Lateral spine radiographs were performed at baseline and at 3 years, and fractures were assessed semiquantitatively.

STATISTICAL ANALYSIS

All analyses were performed using an intention-to-treat approach. For women who withdrew from the study before the 36-month visit, the last available observation was carried forward to subsequent visits. For all randomized subjects, baseline characteristics were compared across therapy groups using analysis of variance for continuous characteristics (eg, age) and Pearson χ² for discrete variables (eg, prior estrogen therapy). Analysis of variance was used to evaluate changes and percentage changes in BMD and included a term for therapy and country. For BMD end points, least squares analysis was used to test each pairwise comparison at the 2-sided P = .03 level of significance, reflecting an adjustment for one interim analysis. The results reflecting changes and percentage changes in the concentrations of biochemical markers of bone turnover and serum lipids were skewed (as assessed by the Shapiro-Wilk W test); therefore, the measurements were ranked and then analyzed. Standard errors for median changes in bone turnover and serum lipid concentrations were estimated using the d-delete jackknife methods¹¹,¹² and 2-sided statistical tests. Correlation between changes in bone density and changes in markers of bone turnover were assessed using Pearson product moment correlation coefficients. Rates of occurrences of adverse events were analyzed using Cochran-Mantel-Haenszel test, controlling for country.

RESULTS

A flowchart showing the disposition of the study subjects is given in Figure 1. Clinical and laboratory characteristics of the study subjects at baseline are set out in Tables 1, 2, and 3. There were no significant differences between the groups. Most women (95.6%) were white. Sixty percent of subjects were still taking study medication at 3 years, the mean duration of medication use being 2.2 years. There were no significant differences between the groups in the number of women attending for each of the study visits. Causes of discontinuation were mainly adverse events (17.6% of the original cohort), personal reasons (17.3%), and protocol violations (5.0%). There were no differences among the therapy groups with respect to the number of women.
who discontinued the study drug (range, 38.0% in the CEE group to 42.8% in the placebo group). The percentage of women missing more than 20% of study medication was similar across the groups (range, 9.6%-13.9%, \( P = .71 \)).

**BONE TURNOVER**

**Figure 2** shows changes in markers of bone turnover among the treatment groups during the study. In the placebo group, there was a 15.0% reduction in serum osteocalcin at 36 months (\( P < .05 \)), probably as a result of the use of calcium supplements. The median reductions in serum osteocalcin for the 2 raloxifene dosages were 27.0% and 28.4%, while that for CEE was 47.1%. Each active therapy was different from placebo throughout the study (\( P < .001 \) for all time points). At end point, raloxifene reduced osteocalcin (relative to placebo) by 12.0% and 13.4% for the 60 mg/d and 150 mg/d dosages, respectively, and CEE reduced it 32.1% below placebo.

The other index of osteoblast function assessed, serum bone-specific alkaline phosphatase, showed a similar pattern, with the 2 raloxifene dosages reducing levels 5.1% and 11.2% below the placebo group, whereas CEE reduced levels 36.8% below placebo. Urinary excretion of the C-telopeptide of type I collagen was not different from placebo in the group receiving 60 mg/d of raloxifene, was about 15% below placebo in the group.
receiving 150 mg/d of raloxifene (significant at some intermediate time points only), and was suppressed below all other groups by CEE (P < .001).

BONE MINERAL DENSITY

**Figure 3** shows changes in BMD among the treatment groups during the study. Bone mineral density in the lumbar spine progressively declined in the placebo group, the mean loss amounting to 2.0% during 3 years (P < .05). In the 2 raloxifene groups, bone density was maintained at or near baseline values, whereas there was a gain of 4.6% in the subjects receiving CEE (P < .001). The effects in the raloxifene groups were different from those observed in the CEE and placebo groups (P < .001).

The pattern of BMD response was similar in the total hip, with a loss of 1.3% in the placebo group (P < .05), maintenance of density in the 2 raloxifene groups, and a progressive gain in density in the CEE group, amounting to 3.0% at 36 months (P < .001). With the exception of the 2 raloxifene groups, all groups were significantly different from one another (P < .001). Similar patterns of response were seen in the subregions of the proximal femur (femoral neck, trochanter, intertrochanteric region, and Ward triangle; data not shown). Analysis restricted to those subjects who completed the full 3 years of the study produced essentially the same results (data not shown). There was no interaction between subjects’ ovariectomy status and the response to the treatments for hip or spine BMD.

Across the entire cohort, the changes in bone density were related to those in markers of bone turnover, the correlation coefficients tending to be more significant in the spine (−0.30 < r < −0.47) than in the femoral neck (−0.29 < r < −0.14). When changes in bone density were assessed in multiple regression analyses, which included changes in each of the markers, the differences between the 4 therapy groups remained significant (P < .001 at the spine and the femoral neck). This implies that differences in antiresorptive effects do not entirely account for the differences in bone density effects, although the imprecision of all variables in this analysis should lead to caution in this interpretation.

LIPIDS

Changes in circulating lipid concentrations were near maximal at 3 months, and no further changes occurred subsequently. At 3 years, median total cholesterol was not changed from baseline in the placebo or CEE groups, but was reduced by both dosages of raloxifene (60 mg/d: −4.7%, and 150 mg/d: −7.2%; P < .05 for each vs placebo). The effects on the HDL and LDL components of cholesterol are shown in **Figure 4**. Neither raloxifene dosage affected HDL cholesterol, whereas CEE increased median HDL cholesterol to 13.4% above placebo at 3 years (P < .001). Each of the active treatments reduced LDL cholesterol below placebo levels (P < .001 at most time points), but they were not significantly different from one another. These combined effects resulted in changes in LDL/HDL ratios at 3 years as follows: placebo, 3.2%; 60 mg/d of raloxifene, −6.1%; 150 mg/d of raloxifene, −6.9%; and CEE, −17.8%. All these changes were significantly dif-

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**Table 2. Baseline Bone Density and Bone Turnover**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Raloxifene, 60 mg/d</th>
<th>Raloxifene, 150 mg/d</th>
<th>CEE, 0.625 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone density*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine, g/cm²</td>
<td>0.97 ± 0.12</td>
<td>0.97 ± 0.12</td>
<td>0.97 ± 0.12</td>
<td>0.96 ± 0.11</td>
</tr>
<tr>
<td>Total hip, g/cm²</td>
<td>0.88 ± 0.12</td>
<td>0.89 ± 0.12</td>
<td>0.90 ± 0.11</td>
<td>0.88 ± 0.12</td>
</tr>
<tr>
<td>Bone turnover†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteocalcin, µg/L</td>
<td>26.2</td>
<td>25.9</td>
<td>26.8</td>
<td>25.8</td>
</tr>
<tr>
<td>Bone-specific alkaline phosphatase, µg/L</td>
<td>10.3</td>
<td>11.5</td>
<td>9.6</td>
<td>9.8</td>
</tr>
<tr>
<td>C-telopeptide-creatinine ratio, µg/mmol</td>
<td>208</td>
<td>203</td>
<td>207</td>
<td>196</td>
</tr>
</tbody>
</table>

Abbreviation: CEE, conjugated equine estrogen.

*Bone density data are expressed as mean ± SD.

†Bone turnover data are expressed as the median value for each group.

**Table 3. Median Baseline Serum Lipids**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Raloxifene, 60 mg/d</th>
<th>Raloxifene, 150 mg/d</th>
<th>CEE, 0.625 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL*</td>
<td>232</td>
<td>232</td>
<td>232</td>
<td>236</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL*</td>
<td>147</td>
<td>151</td>
<td>151</td>
<td>151</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL*</td>
<td>58</td>
<td>58</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>97</td>
<td>106</td>
<td>97</td>
<td>89</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>2.5</td>
<td>2.7</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Apolipoprotein A1, mg/dL</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>140</td>
<td>140</td>
<td>130</td>
<td>140</td>
</tr>
</tbody>
</table>

Abbreviations: CEE, conjugated equine estrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, by 0.0113; and apolipoprotein A1 and B to grams per liter, by 0.01.
ferent from zero, the active therapies were each different from placebo ($P < .001$), and effects of CEE were different from those of both raloxifene groups ($P < .001$).

Triglyceride concentrations were stable in the placebo group. In both raloxifene groups, triglyceride concentrations increased from baseline (4.9% and 8.0% for the 60 mg/d and 150 mg/d dosages, respectively; $P < .002$), although these changes were not significantly different from placebo at 3 years. Triglyceride concentrations were greater in the CEE group (24.6% median increase above baseline at 3 years; $P < .003$) than in the raloxifene groups.

Apolipoprotein A1 concentrations were stable throughout the study in the placebo group, increased slightly in the raloxifene groups (median change at 3 years, 2.9% and 1.6% for 60 mg/d and 150 mg/d, respectively; $P < .05$ for both), and showed a larger increase in the CEE group (15.3% above baseline at 3 years, different from all other groups; $P < .05$).

There were some fluctuations in concentrations of apolipoprotein B throughout the study, but at 3 years the change from baseline in the CEE group was not different from that observed with placebo (−2.9% and −4.1% from baseline, respectively), whereas there were greater decreases in the groups receiving 60 mg/d and 150 mg/d of raloxifene (−7.3% and −9.2% from baseline, respectively; $P < .05$). There was no interaction between subjects’ ovariectomy status and the response to the treatments for any of the lipid variables.

ADVERSE EVENTS

Study medications were generally well tolerated. There were no significant differences among the 4 groups in the proportion of women reporting adverse events or serious adverse events, nor were there differences in the proportion of women leaving the study because of an adverse event. Six adverse events were reported, at rates that
were significantly different among the groups (Table 4). Hot flashes were reported less frequently in the CEE group compared with each of the other groups (P ≤ .001), and more frequently in the group receiving 150 mg/d of raloxifene compared with the others (P ≤ .04), but were not significantly different between the placebo group and the group receiving 60 mg/d of raloxifene. Leg cramps were also more common in those receiving raloxifene (P ≤ .03 for either dosage compared with placebo or CEE). In contrast, breast pain and enlargement were more common in the women receiving CEE (P ≤ .02 compared with the other groups). Urinary incontinence was also more common in those receiving CEE (P ≤ .01 compared with the other groups). Hernias occurred less frequently in those receiving 150 mg/d of raloxifene or CEE, compared with placebo (P = .03). There were no significant differences between groups in the incidence of myocardial infarction (placebo, 0; 60 mg/d of raloxifene, 1; 150 mg/d of raloxifene, 1; and CEE, 1) or vertebral fracture (placebo, 1; 60 mg/d of raloxifene, 3; 150 mg/d of raloxifene, 1; and CEE, 1).

**COMMENT**

This is one of few studies to directly compare the effects of treatments widely used in the management of osteoporosis. Its findings are broadly consistent with previous data relating to raloxifene, other selective estrogen receptor modulators, and estrogen. Modest changes in bone turnover markers have been reported with raloxifene, whereas those associated with the use of estrogen have tended to be larger, as found in the present study. These results on the relative effects of raloxifene and estrogen on bone markers are consistent with those reported in a short-term study. A study comparing the effects of raloxifene and estrogen on calcium kinetics also found greater remodeling suppression with estrogen.

Previous studies have demonstrated a consistent effect of raloxifene on lumbar spine BMD. Increases in the range of 1% to 3% from baseline and 2% to 3% above placebo have been observed during 2- to 3-year treatment periods, the difference being slightly less at the femoral neck. In the present study, raloxifene did not increase BMD above baseline but maintained it, producing a difference from placebo similar in magnitude to that observed in previous studies. Therefore, the apparent differences in BMD changes with raloxifene therapy between the various studies are likely attributable to differences in the rates of bone loss in the placebo groups. The same variability is seen in studies of estrogen, but compared with placebo, estrogen increases lumbar spine BMD by about 5% to 6% over a similar treatment period. Therefore, the present data confirm that estrogen therapy is associated with greater increases in lumbar spine BMD than are seen with raloxifene. This difference in BMD effects is consistent with the similar difference between these 2 agents in their effects on bone turnover, in that raloxifene affects each of these indexes to about one third the extent observed for estrogen.

It is unknown whether the differences in the effects of raloxifene and estrogen on surrogate markers of bone efficacy translate into differences in fracture risk reduction. Although low BMD predicts increased fracture risk in osteoporosis, it is controversial how well increases in BMD with antiresorptive therapy predict fracture risk. Therefore, some authors point out that antiresorptive agents that produce different BMD changes result in risk reductions for vertebral fracture that are not significantly different from each other, whereas others have shown a direct relationship between bone density changes and antifracture efficacy. There are wide confidence intervals on all such assessments of fracture risk reduction, which is why such contradictory interpre-

![Figure 4. Effect of treatment with raloxifene (60 mg/d or 150 mg/d), 0.625 mg/day of conjugated equine estrogen, or placebo on circulating lipid concentrations. A, High-density lipoprotein cholesterol. Conjugated equine estrogen was different from placebo (P < .001). B, Low-density lipoprotein cholesterol. All active treatments were less than placebo (P < .001 at most time points) but not significantly different from one another. C, Triglycerides. Conjugated equine estrogen was greater than all other groups at 3 years (P < .003); raloxifene was not different from placebo.](#)
tions are possible. The same limitation applies to the recent observation in the MORE trial that BMD changes observed with raloxifene therapy were poor predictors of subsequent vertebral fracture risk reduction.27

There is similar uncertainty with respect to nonvertebral fractures. Numerous observational studies suggest that hormone therapy reduces the risk of these fractures. Although a large randomized study in a special population (Heart and Estrogen/Progestin Replacement Study) has not shown a nonvertebral fracture effect for hormone therapy,28 a recently published meta-analysis29 suggests that such an effect may be present, and this is confirmed by the Women’s Health Initiative.30 To date, no significant effect on nonvertebral fractures has been demonstrated with raloxifene. Therefore, the available data do not allow firm conclusions with respect to whether biochemical and densitometric changes associated with raloxifene and hormone therapy are indicative of their antifracture efficacy.

Whereas raloxifene and estrogen differ in their effects on bone metabolism only in degree, they produce distinct patterns of effects on circulating lipids. Therefore, raloxifene has no effect on HDL cholesterol and a small effect on apolipoprotein A1, whereas estrogen increases both. Their effects on LDL cholesterol are similar. In contrast, estrogen produces substantial increases in triglyceride concentrations, whereas the effects of both dosages of raloxifene are minor. The triglyceride effect of CEE may have artifactually increased apolipoprotein A1, whereas estrogen in-
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ized trial of nasal spray salmon calcitonin in postmenopausal women with es-
tablished osteoporosis: the Prevent Recurrence of Osteoporotic Fractures study. 
26. Wansch R, Miller PD. Antifracture efficacy of antiresorptive agents are related 
between bone mineral density and incident vertebral fracture risk with raloxi-
therapy on clinical fractures and height loss: the Heart and Estrogen/Progestin 
29. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of 
nonvertebral fractures: a meta-analysis of randomized trials. JAMA. 2001;285:
2891-2897.
30. Walmsley TA, Grant S, George PM. Effect of plasma triglyceride concentrations 
on the accuracy of immunoturbidimetric assays of apolipoprotein B. Clin Chem.
1991;37:748-753.
reduce major cardiovascular risk factors in healthy postmenopausal women: a 
2-year, placebo-controlled study. Arterioscler Thromb Vasc Biol. 1999;19:2993-
3000.
and raloxifene on C-reactive protein and homocysteine in healthy postmeno-
pausal women: a randomized, controlled trial. J Clin Endocrinol Metab. 2000;
33. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regi-
mens on heart disease risk factors in postmenopausal women: the Postmeno-
pausal Estrogen/Progestin Interventions (PEPI) trial [published correction ap-
34. Speroff L, Rowan J, Symons J, Genant H, Wilborn W. The comparative effect on 
bone density, endometrium, and lipids of continuous hormones as replacement 
therapy (CHART study): a randomized controlled trial. JAMA. 1996;276:1397-
1403.
35. De Leo V, la Marca A, Morgante G, Lanzetta D, Setacci C, Petraglia F. Random-
ized control study of the effects of raloxifene on serum lipids and homocysteine 
36. Hulley S, Grady D, Bush T, et al, Heart and Estrogen/Progestin Replacement Study 
(HERS) Research Group. Randomized trial of estrogen plus progesterin for sec-
condary prevention of coronary heart disease in postmenopausal women. JAMA. 
6.8 years of hormone therapy. JAMA. 2002;288:49-57.
38. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replace-
342:522-529.
40. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomo-
tor symptoms and vaginal atrophy with lower doses of conjugated equine es-
41. Fantl JA, Bump RC, Robinson D, McClish DK, Wyman JF, Continence Program 
for Women Research Group. Efficacy of estrogen supplementation in the treat-
42. Jackson S, Shepherd A, Brookes S, Abrams P. The effect of oestrogen supple-
mentation on post-menopausal urinary stress incontinence: a double-blind placebo-
43. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T. Postmeno-
pausal hormones and incontinence: the Heart and Estrogen/Progestin Replace-
44. Goldstein SR, Neven P, Zhou L, Taylor VL, Ciacca AV, Piouffe L.Raloxifene effect 