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ORIGINAL REPORT

Quality of Life in MAP.3 (Mammary Prevention 3): A Randomized, Placebo-Controlled Trial Evaluating Exemestane for Prevention of Breast Cancer

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
Exemestane, a steroidal aromatase inhibitor, reduced invasive breast cancer incidence by 65% among 4,560 postmenopausal women randomly assigned to exemestane (25 mg per day) compared with placebo in the National Cancer Institute of Canada (NCIC) Clinical Trials Group MAP.3 (Mammary Prevention 3) trial, but effects on quality of life (QOL) were not fully described.

Patients and Methods
Menopause-specific and health-related QOL were assessed by using the four Menopause-Specific Quality of Life Questionnaire (MENQOL) domains and the eight Medical Outcomes Study Short Form Health Survey (SF-36) scales at baseline, 6 months, and yearly thereafter. MENQOL questionnaire completion was high (88% to 98%) in both groups at each follow-up visit. Change scores for each MENQOL and SF-36 scale, calculated at each assessment time relative to baseline, were compared by using the Wilcoxon rank-sum test. Clinically important worsened QOL was defined as a MENQOL change score increase of more than 0.5 (of 8) points and an SF-36 change score decrease of more than 5 (of 100) points from baseline.

Results
Exemestane had small negative effects on women's self-reported vasomotor symptoms, sexual symptoms, and pain, which occurred mainly in the first 6 months to 2 years after random assignment. However, these changes represented only a small excess number of women being given exemestane with clinically important worsening of QOL at one time or another; specifically, 8% more in the vasomotor domain and 4% more each in the sexual domain and for pain. No other between-group differences were observed. Overall, slightly more women in the exemestane arm (32%) than in the placebo arm (28%) discontinued assigned treatment.

Conclusion
Exemestane given for prevention has limited negative impact on menopause-specific and health-related QOL in healthy postmenopausal women at risk for breast cancer.

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INTRODUCTION

The American Society of Clinical Oncology breast cancer risk reduction guideline update recently added exemestane as an intervention that "should be discussed" as an alternative to tamoxifen and/or raloxifene to reduce invasive breast cancer risk in postmenopausal women.[1] This recommendation was made in light of findings from the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Mammary Prevention 3 (MAP.3) placebo-controlled randomized prevention trial in which exemestane—a steroidal aromatase inhibitor—reduced invasive breast cancers by 65% among healthy postmenopausal women.[2] There were no significant differences in skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths between randomization groups.[2] Nonetheless, the potential for negative influence of an aromatase inhibitor on menopausal symptoms, musculoskeletal pain, and overall quality of life presents a concern.[3,4] We previously reported summary information about the minimal quality-of-life differences between randomization groups in the MAP.3 trial resulting from exemestane therapy. We now provide detailed description of

the extent to which exemestane was associated with negative changes in menopause-specific and general health-related quality-of-life measures throughout the study.

PATIENTS AND METHODS

Design

The MAP.3 study design and conduct were previously described.[2] In this multicenter trial 4,560 postmenopausal women were randomly assigned to exemestane (25 mg) or placebo orally once per day for up to 5 years. The primary end point was invasive breast cancer incidence, and secondary end points were all breast cancers (invasive and ductal carcinoma in situ), clinical skeletal fractures, cardiovascular events, and menopause-specific and general health-related quality of life. The trial was approved by health regulatory authorities and institutional review boards at participating centers. All participants gave written, informed consent.

Population

Women were eligible if they were postmenopausal, defined as age $\geq$ 50 years with no menses for at least 12 months; age less than 50 years with no menses within the past 12 months (spontaneous or secondary to hysterectomy) and with estrogen level within the institution's postmenopausal range; or with bilateral oophorectomy history. Additional eligibility requirements included completing baseline quality-of-life questionnaires and having one or more among the following: calculated Gail score[5] more than 1.66%, age $\geq$ 60 years, prior atypical ductal or lobular hyperplasia, lobular carcinoma in situ, or prior ductal carcinoma in situ treated with mastectomy.

Quality-of-Life Assessment

Quality of life was assessed before random assignment, at 6 months, and annually thereafter by using the Menopause-Specific Quality of Life Questionnaire (MENQOL)[6] and the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) version 2[7-9] for health-related quality of life. Both instruments have been established as valid, reliable, and sensitive to change.[9,10]

The MENQOL assesses the degree to which menopausal symptoms are bothersome in four domains: vasomotor (three items), sexual (three items), physical (seven items), and psychosocial (16 items). Symptoms assessed included hot flashes, night sweats, vaginal dryness, and sexual dysfunction, aching muscles or joints, feeling depressed, difficulty sleeping, weight gain, and dry skin. At each assessment, participants were asked if they had experienced symptoms or problems within the past month (no, yes), and if they had, to rate each on a 7-point scale ranging from "not at all bothered" to "extremely bothered." Ratings were then scored from 1 (no symptoms were present) to 7; the 1 to 7 ratings were recoded as 2 (symptom present but not bothered by it at all) to 8, and perception of being bothered started at 3 and went up to 8 (extremely bothered). MENQOL domain scores were calculated as the mean item scores, with higher scores indicating more bothersome symptoms and less favorable quality of life.

All SF-36 scales and component summaries (Physical Component Summary and Mental Component Summary) were used. The eight scales cover bodily pain (two items), physical functioning (10 items), general health (five items), role-physical (four items), mental health (five items), vitality (four items), social functioning (two items), and role-emotional (three items). The SF-36 scales are scored from 0 to 100, with higher scores representing better quality of life. The Physical Component Summary and Mental Component Summary provide global quality-of-life indicators for the physical and mental domains, respectively.[9]

Statistical Analyses

Following standard practice, a score was calculated for each participant who responded to more than 50% of the scale items. Then, on the basis of all participants with scores for a given scale, the evolution in mean scores for each group was presented as a function of the entire possible score range. Mean change scores from baseline were calculated for all MENQOL and SF-36 subscales, and the Wilcoxon rank-sum test was used to compare the between-group differences in mean within-patient change scores. This latter measure was used to quantify the effect of exemestane on quality of life (Appendix Fig A1, online only). A net negative impact of exemestane on menopausal symptoms and on health-related quality of life was represented by positive net differences on MENQOL domains and negative net differences on SF-36 scales, respectively. Changes measuring 5% to 10% of the scale breadth (MENQOL, score changes of $>$ 0.5 points from baseline; SF-36, $>$ 5 points from baseline) were considered as potentially clinically meaningful.[11] These criteria were also used for defining clinically meaningful net differences in within-patient change between arms.

Women were also compared on the basis of the proportion of women having worsened, improved, or remained stable regarding quality of life relative to baseline.[12] Quality of life was considered worsened if women reported a $\geq$ 0.5-point increase (of 8 points) on MENQOL scores or a $\geq$ 5-point decrease (of 100 points) on SF-36 scores without subsequent improvement. Among those who never worsened, women were considered as having improved if they reported a $\geq$ 0.5-point decrease (of 8 points) on MENQOL scores or a $\geq$ 5-point increase (of 100 points) on SF-36 scores, respectively, at any assessment. The remaining women were considered to have stable quality of life. The χ^2 test was used to compare the distributions of worsened, improved, and stable scores between randomization groups. The "worsening first" approach presented here, rather than "improved first" approach,[2] was a better fit with the primary clinical concerns of women considering chemoprevention and also of their clinicians, because this approach best detects early worsening of quality of life, which is highly relevant to healthy women taking a drug to prevent a health problem from occurring.

Women were considered to be very bothered by menopausal symptoms if they rated a specific MENQOL symptom as 6 to 8 of a total of 8. The three most common symptoms in each domain are reported on the basis of frequency in the exemestane group. Finally, at 12 months, for pain and vasomotor symptoms known a priori to be effects of aromatase inhibitors, we created several new indicators to explore whether women who reported high levels on these symptoms also simultaneously (ie, at the same assessment) reported high levels of interference with capacity to do usual activities as measured by certain health-related quality-of-life questions. Then the proportions of women in each group who were positive for these indicators were compared.

RESULTS

Study Population and Compliance With Quality-of-Life Assessments

Of the 4,560 participants, 4,468 (98%) completed both the MENQOL and SF-36 questionnaires at baseline. The median duration of follow-up was 3 years. By trial design, MAP.3 intervention ended once the required number of invasive breast cancers had occurred and the main trial objective had been analyzed.[2] Consequently, only 39.9% (1,783 of 4,468), 21.7% (970 of 4,468), and 5.2% (230 of 4,468) of participants had accumulated sufficient follow-up time at trial closure to complete quality-of-life questionnaires at 3, 4, and 5 years after random assignment, respectively. Quality-of-life questionnaire compliance was excellent; between 88% and 98% of participants still taking study medication continued to complete these forms at 6 months and years 1, 2, 3, 4, and 5 (Fig 1). In addition, distributions of women's baseline characteristics in each randomization group at 3, 4, and 5 years were still similar to what they were at baseline, and their values were comparable between randomization groups at these three assessment times (data not shown).

Overall, 32% of participants randomly assigned to exemestane and 28% randomly assigned to placebo discontinued assigned treatment, a difference mainly reflecting more women stopping exemestane by 6 months (10.4% *v* 6.5% for placebo). Subsequently, the rates

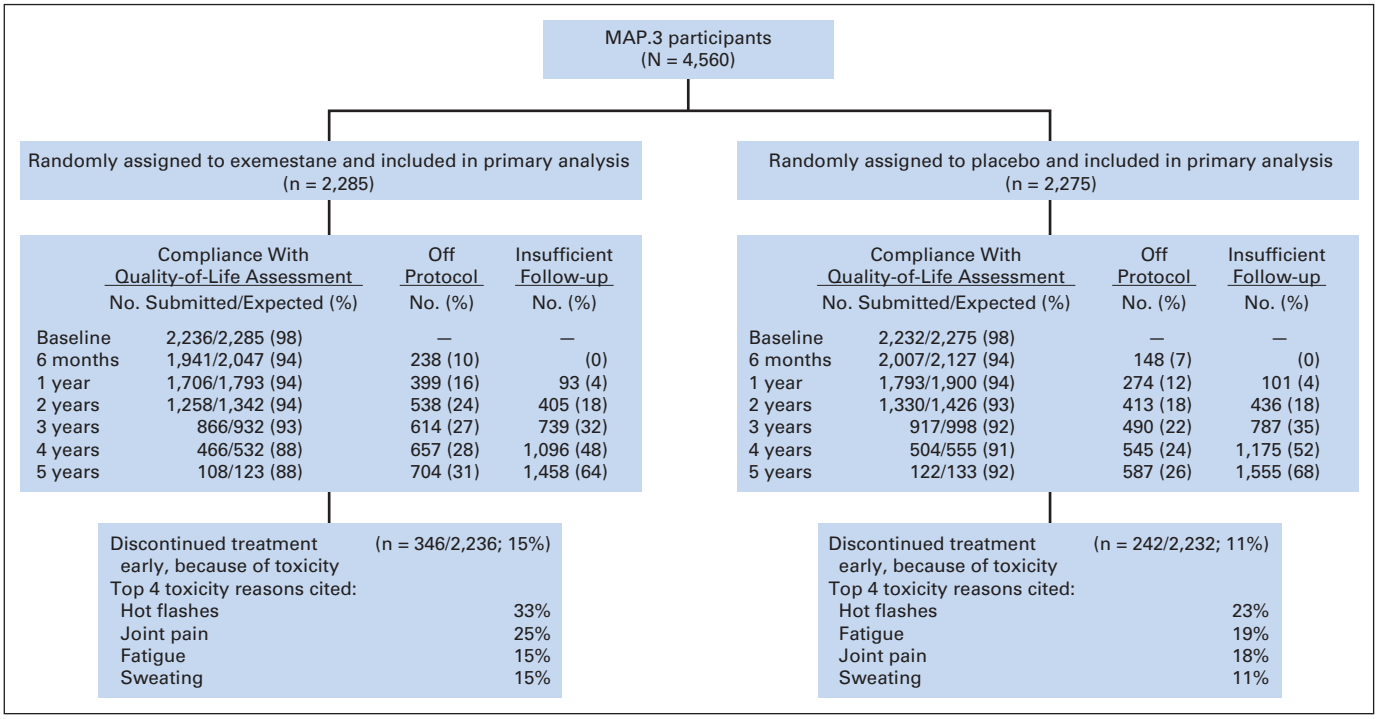

Fig 1. MAP.3 (Mammary Prevention 3) quality of life flowchart.

of medication discontinuation were lower and were similar between randomization groups (data not shown). Generally, adherence to medication was comparable between the two groups, including median duration of study medication, numbers of pills missed, and percentages in each group modifying their treatment dose in a manner in accordance (or not) with protocol guidelines (data not shown).

Baseline Characteristics

Sociodemographic and psychosocial characteristics were well balanced between randomization groups at baseline, and MENQOL and SF-36 scores were closely comparable (Table 1). For mean MENQOL scores in the vasomotor, sexual, physical, and psychosocial domains, scores were between 2.1 and 2.6, indicating little bother from such symptoms at enrollment.

Changes in Symptoms and Quality of Life From Baseline

Women randomly assigned to exemestane consistently had statistically significantly higher vasomotor change scores (all P values $<$ .01) compared with the placebo group. Their vasomotor symptom scores were greatest at 6 months and decreased thereafter (Fig 2A). However, the between-group differences in vasomotor change scores were smaller than those defined a priori as being clinically important. For the MENQOL sexual, physical, and psychosocial domains, respectively (Figs 2B-D), change scores evolved similarly in both groups, and the between-group differences in change scores were almost all approximately 0.1 points (of 8) or smaller.

Women randomly assigned to exemestane had consistently higher SF-36 bodily pain scores showing increased pain starting at 6 months and continuing throughout the study. The changes in levels of bodily pain in the exemestane group approached the threshold for a clinically important change from baseline at 2 and 3 years and reached it by 4 years and beyond. However, the greatest net between-group difference in pain change scores, observed at 2 years, still amounted to only a 1.85-point difference (of 100 points) (Fig 2E) and did not come close to the 5-point threshold. Otherwise, with the exception of social functioning at 4 years, the mean change scores for most SF-36 scales changed in a similar direction and with similar magnitude for women randomly assigned to exemestane or placebo, with net between-group differences well below the 5% threshold for clinically important change (Figs 2E-L). In the psychological scales, net differences up to 4 years after random assignment were all negligible ($<$ 1 of 100 points) for mental health on measures of symptoms of anxiety, depression, and vitality (Figs 2I-J).

During the study, a considerable proportion of women in both the exemestane and placebo groups reported worsening that met a priori definition of clinical importance in menopause-specific or general health-related quality of life, specifically, 37% to 51% for the menopause-related domains and between 46% and 67% on the SF-36 scales (Table 2). For the MENQOL, the principal negative effects of exemestane were vasomotor symptoms, for which 55% of the patients being given exemestane reported worsened vasomotor symptoms compared with 47% of the patients being given placebo (relative risk [RR], 1.17; $P < .001$; Table 2). The sexual domain was also somewhat negatively affected by exemestane (39% and 35%, respectively; RR, 1.15; $P = .04$). Only one SF-36 scale, bodily pain, showed a consistent but small absolute difference in the proportion of women reporting worsened pain, disfavoring exemestane (66% v 62%; RR, 1.07; $P =$ .01; Table 2).

When women were compared on the basis of very or extremely bothersome ($\geq$ 6 of 8 points) MENQOL symptoms stratified by age, between-group differences were greatest for specific symptoms in the

Table 1. Baseline Characteristics of 4,468 Postmenopausal Women Who Consented to Participate in the MAP.3 Breast Cancer Prevention Trial and Who Completed Baseline Quality-of-Life Assessments

Characteristic	Exemestane (n = 2,236)				Placebo (n = 2,232)			
	No.	%	Mean	SD	No.	%	Mean	SD
Age, years								
Median	62.5				62.4			
Range	39-88				37-90			
< 60	721	33.2			691	30.1		
White race/ethnicity	2,089	93.4			2,083	93.3		
BMI								
Median	27.9				28.1			
Range	15.9-54.3				16.3-65.4			
Gail score								
Median	2.3				2.3			
Range	0.6-21.0				0.6-15.1			
Prior HRT	1,292	57.8			1,306	58.5		
Education level								
University degree(s)	934	41.8			961	43.1		
College, some university	698	31.2			449	31.1		
High school diploma	360	16.1			338	15.1		
Elementary school/some high school	239	10.7			233	10.5		
Marital status								
Married	1423	63.6			948	64.8		
Divorced/separated	353	15.8			238	16.2		
Single	190	8.5			182	8.2		
Widowed	268	12.0			255	11.4		
Paid job or self-employed	1,091	48.8			1,097	49.1		
Average No. of confidantes								
Median	4				4			
Range	0-50				0-50			
MENQOL domains								
Vasomotor			2.3	1.6			2.4	1.6
Sexual			2.1	1.6			2.1	1.6
Physical			2.6	1.2			2.5	1.1
Psychosocial			2.2	1.2			2.2	1.2
SF-36 scales and component summaries								
Bodily pain			71.4.	22.0			71.4	21.6
Physical health			81.1	20.1			81.9	19.0
General health			78.4	16.3			78.8	16.4
Role function, physical			84.4	21.2			85.5	19.6
Mental health			72.6	12.0			72.9	11.7
Vitality			64.5	13.7			65.1	13.5
Social function			92.0	15.9			91.7	16.0
Role function, emotional			90.6	17.0			91.0	16.6
PCS			49.7	8.2			50.0	7.9
MCS			52.5	6.3			52.4	6.2

Abbreviations: BMI, body-mass index; HRT, hormone replacement therapy; MAP.3, Mammary Prevention 3; MCS, Mental Component Summary; MENQOL, Menopause-Specific Quality of Life Questionnaire; PCS, Physical Component Summary; SD, standard deviation; SF-36, Medical Outcomes Study Short Form Health Survey.

vasomotor and physical spheres (Table 3). Bothersome vasomotor symptoms were generally more prevalent in the younger age group than in the older age group. However, in both age groups, more women taking exemestane were severely bothered by vasomotor symptoms at 6 months or at any time following random assignment. The overall prevalence of bothersome sexual symptoms was higher in women younger than age 60, and negative differences attributable to exemestane were seen only in this age group. For the physical domain, the main negative effects of exemestane were for "aching muscles and joints" and "difficulty sleeping," and this did not differ by age group. The frequency of the other 14 symptoms in the physical domain were similar in the two randomization groups (data not shown), as were the percentages with high domain scores (Table 3). No clear effects of exemestane on bothersome symptoms in the psychosocial domain were observed in either age group. Although being severely bothered by "poor memory" was the second most frequently reported symptom in this domain, there were no between-group differences attributable to exemestane at either time or by age group.

After 1 year, 1.9% of women taking exemestane reported a vasomotor score of $\geq$ 6 of 8 and that their health was

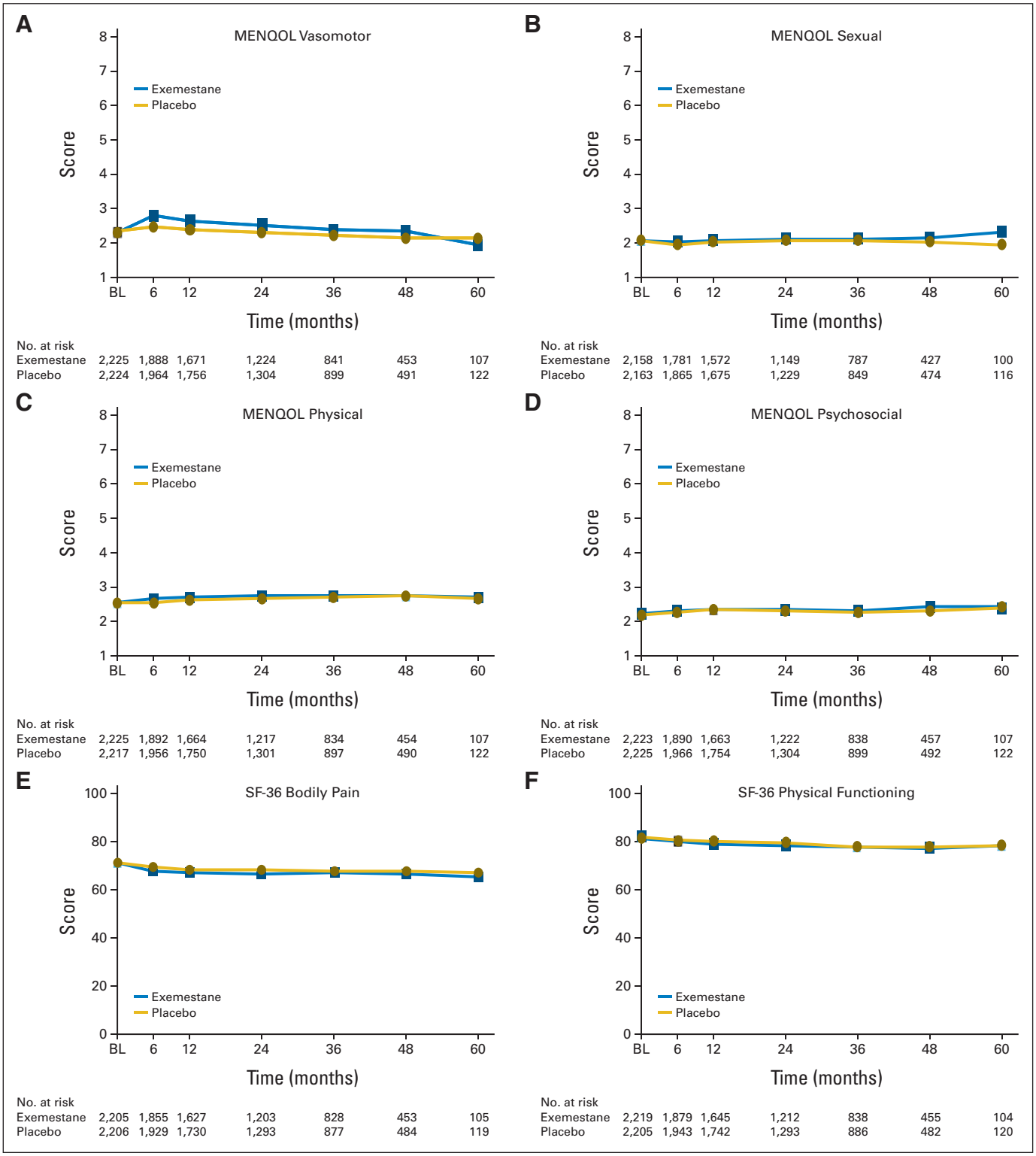

Fig 2. Evolution of mean Menopause-Specific Quality of Life Questionnaire (MENQOL) and Medical Outcomes Study Short Form Health Survey (SF-36) scores over time, comparing exemestane and placebo groups.

"somewhat/much worse" than a year ago compared with 1.6% of women receiving placebo. There was also no difference when the MENQOL score criterion included lower vasomotor scores (scores $\geq$ 5 of 8; 3.6% *v* 3.5%, respectively). The proportions of women simultaneously reporting "severe/very severe" bodily pain (SF-36 question 8) and that pain interfered "quite a bit/extremely" with normal work activities (SF-36 question 7) were 11.7% for the exemestane group versus 10.7% for the placebo

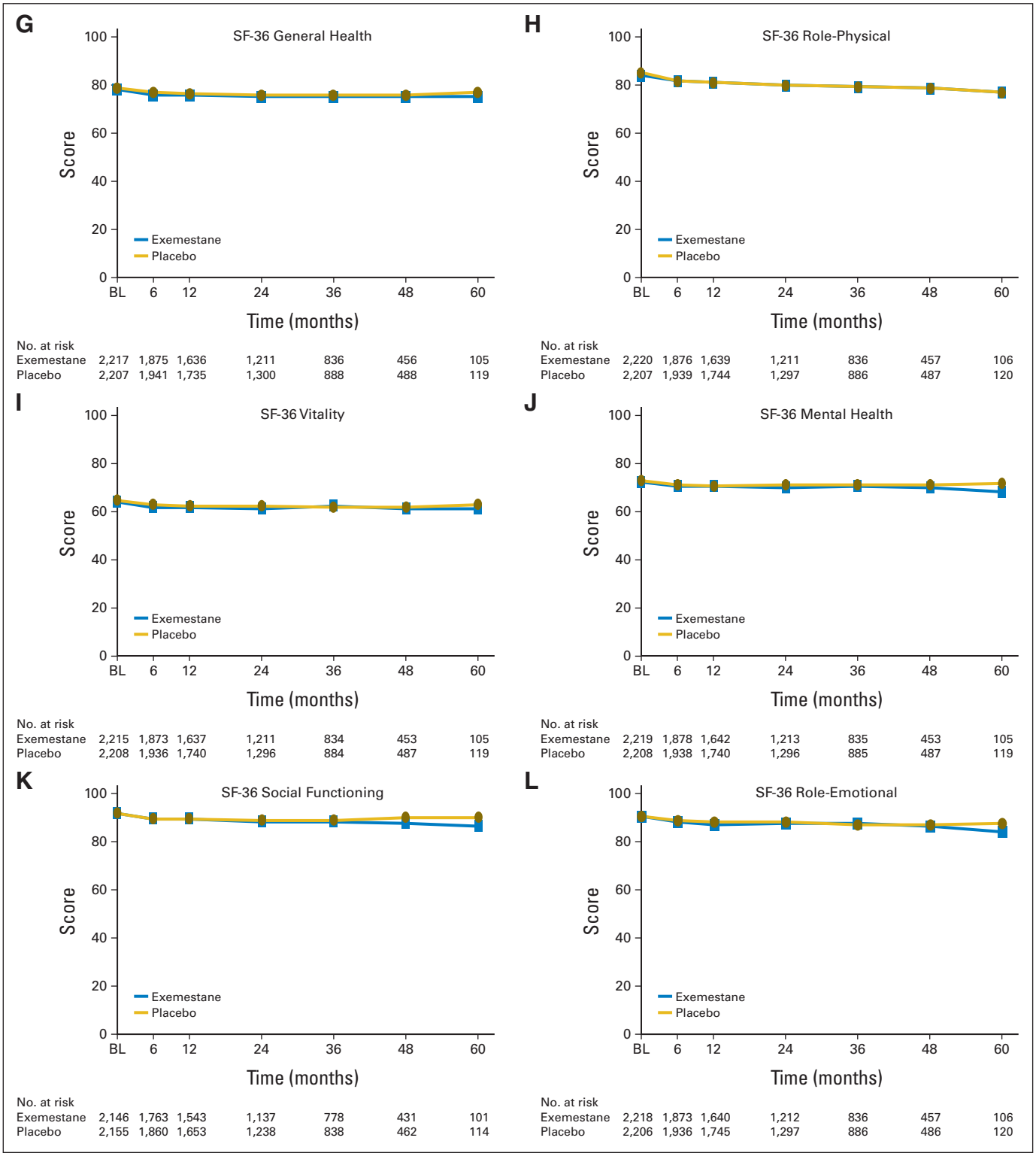

Fig 2. Continued.

group. When criteria included moderate pain and moderate interference, again no difference was found (35.3% *v* 33.5%, respectively). The same analyses with pain but with SF-36 question 6 (interference with normal social activities) also found no detriment attributable to exemestane (4.7% *v* 4.7%, respectively, for the severe analysis and 18.8% *v* 17.8%, respectively, for the relaxed criteria). No between-group differences were found when severe MENQOL aches in muscles and joints were assessed in relation to interference with usual activities (data not shown).

Table 2. Clinically Important Worsening of Menopause-Specific or General Health-Related Quality of Life, Comparing Women Randomly Assigned to Exemestane or Placebo

	Clinically Important Worsening Reported											
	Exemestane						Placebo					
	First 6 Months		Year 1 (cumulative*)		Ever (cumulative*)		First 6 Months		Year 1 (cumulative*)		Ever (cumulative*)	
Domain	Total No. of Patients	%	Total No. of Patients	%	Total No. of Patients	%	Total No. of Patients	%	Total No. of Patients	%	Total No. of Patients	%
MENQOL												
Vasomotor	1,888†	39	1,959†	49	1,960†	55	1,964	29	2,040	39	2,054	47
Sexual	1,774‡	20	1,876‡	29	1,898‡	39	1,860	17	1,967	26	1,984	35
Physical	1,892	29	1,959	41	1,965	52	1,956	26	2,034	39	2,060	50
Psychosocial	1,890	27	1,959	39	1,967	50	1,966	26	2,041	39	2,054	50
SF-36												
Bodily pain	1,855‡	41	1,955‡	56	1,957‡	66	1,929	37	2,041	51	2,053	62
Physical functioning	1,879	39	1,946	52	1,962	63	1,943	37	2,028	50	2,018	62
General health	1,875	38	1,955	50	1,949	61	1,941	36	2,038	50	2,028	60
Role-physical	1,876	36	1,953	50	1,986	63	1,939	34	2,033	49	2,051	61
Mental health	1,861	27	1,957	37	1,965	49	1,916	25	2,030	36	2,037	48
Vitality	1,873‡	45	1,955	58	1,978	68	1,936	43	2,016	57	2,058	67
Social functioning	1,756	24	1,867	34	1,879	46	1,838	24	1,973	34	1,989	46
Role-emotional	1,889	27	1,951	38	1,960	50	1,930	25	2,032	36	2,038	47
PCS	1,752	19	1,834	29	1,849	42	1,794	18	1,934	27	1,959	38
MCS	1,703	18	1,834	27	1,849	35	1,800	17	1,923	26	1,959	35

NOTE. Worsened: ≥ 0.5-point increase (of 8 points) on Menopause-Specific Quality of Life Questionnaire (MENQOL) scores or ≥ 5-point decrease (of 100 points) on Medical Outcomes Study Short Form Health Survey (SF-36) scores, without subsequent improvement. Improved: among those never worsened, ≥ 0.5-point decrease (of 8 points) on MENQOL scores or ≥ 5-point increase (of 100 points) on SF-36 scores at any assessment. Stable: all women not worsened or improved.

Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary.

*Cumulative: at 1 year, worsening noted at either 6 months or 1 year; ever, worsening at any assessment during follow-up.

†$P < .001$ compared with placebo.

‡$P < .05$ compared with placebo.

DISCUSSION

In this randomized, placebo-controlled chemoprevention trial among healthy postmenopausal women in which exemestane reduced invasive breast cancer incidence by 65%, exemestane had some negative influence on vasomotor symptoms, mainly among women age younger than 60 years and on the two MENQOL symptoms related to bodily pain for both age groups. Otherwise differences seen on other dimensions of menopause-specific or general health-related quality of life, including mental health, were smaller than those prospectively defined as being clinically meaningful. Thus, overall health-related quality of life, including women's perceptions of their health and their usual work or social activities, even when these symptoms were present, was not negatively affected by exemestane use.

Several factors may have influenced the low impact of exemestane on quality of life. Women with the most severe symptoms were more likely to discontinue the trial early and therefore not be represented in longer follow-up analyses. Despite a small excess of early discontinuation in women receiving exemestane, the overall proportion of women who remained in the trial up until the final analysis—68% taking exemestane and 72% taking placebo—indicates that our findings represent those from a majority of participants and supports good tolerance for exemestane use in a prevention setting. In addition, therapy discontinuation specifically due to toxicity is an additional clinically relevant measure of the severity of adverse effects in this population of healthy women. In the MAP.3 trial, although this was somewhat more common in the exemestane group (15.4% *v* 10.8%, respectively), the difference was only 4.6%.[2] Perhaps a greater pain effect from exemestane could have been expected across all measures, given the negative influence of aromatase inhibitors on joint pain in adjuvant trials.[13,14] One issue could be that the SF-36 bodily pain scale, composed of two pain-related questions, was not sensitive enough in this setting, although the single items in the MENQOL related to pain did capture differences. However, we also found no between-group differences even when the co-occurrence in the same woman of both severe SF-36 bodily pain and strong negative effects on social and work activities was assessed, supporting the absence of a clinically important effect on pain. Finally, these favorable findings for exemestane use in MAP.3 could reflect differences in risk for aromatase-associated musculoskeletal symptoms between breast cancer and breast cancer-free populations. Younger women and those with pre-existing joint symptoms, prior radiation therapy, or prior chemotherapy experience are more likely to have aromatase inhibitor–associated joint symptoms.[15,16] Because MAP.3 participants were somewhat older and had no cancer therapy experience, their tolerance for exemestane could reasonably be higher. In any event, even in the adjuvant setting, exemestane use has had no significant overall negative impact on quality of life.[17,18]

Study limitations include the relatively short mean duration of the 36-month intervention, with only 5% of women accumulating sufficient follow-up to complete the 5-year assessment. For transparency, we show 5-year results but give them relatively little weight because numbers are

Table 3. Incidence (%) of Three Most Bothersome Symptoms and Domain Scores Rated 6 or Higher in Each MENQOL Domain, According to Age at Baseline

MENQOL Domain	No. of Items in Domain	Age Younger Than 60 Years						Age 60 Years or Older					
		In First 6 Months			Since Random Assignment			In First 6 Months			Since Random Assignment		
		Exemestane (n = 623)	Placebo (n = 617)	Excess Percentage Due to Exemestane	Exemestane (n = 654)	Placebo (n = 654)	Excess Percentage Due to Exemestane	Exemestane (n = 1,318)	Placebo (n = 1,390)	Excess Percentage Due to Exemestane	Exemestane (n = 2,015)	Placebo (n = 1,442)	Excess Percentage Due to Exemestane
Vasomotor	3												
Hot flashes		26.3	17.5	+8.8	36.9	27.8	+9.1	12.4	8.1	+4.3	19.6	13.8	+5.8
Night sweats		23.9	15.7	+8.2	32.6	26.0	+6.6	11.0	6.9	+4.1	17.2	12.6	+4.6
Sweating		18.3	14.3	+4.0	28.6	23.6	+5.0	10.3	7.5	+2.8	18.1	13.6	+4.5
Domain score ≥ 6 of 8†		15.9	9.6	+6.3	22.2	15.6	+6.6	6.4	3.2	+3.2	10.3	6.4	+3.9
Sexual	3												
Vaginal dryness during intercourse		16.9	12.7	+4.3	29.1	24.9	+4.2	8.6	9.6	−1.0	15.9	16.4	−0.5
Avoiding intimacy		11.4	7.5	+3.9	21.4	17.9	+3.5	5.3	5.7	−0.4	10.9	11.8	−0.9
Change in sexual desire		10.6	7.3	+3.3	22.8	16.7	+6.1	5.3	5.5	−0.2	11.0	11.1	−0.1
Domain score ≥ 6 of 8		8.2	5.8	+2.4	15.1	13.6	+1.5	2.0	3.1	−1.1	5.3	6.2	−0.9
Physical	16												
Aching in muscles and joints		29.9	24.1	+5.8	46.3	42.4	+3.9	29.3	23.1	+6.2	48.3	42.3	+6.0
Difficulty sleeping		24.4	20.4	+4.0	40.2	34.0	+6.3	20.3	14.9	+5.4	33.7	27.7	+6.0
Feeling tired or worn out		18.3	15.7	+2.6	30.3	30.9	−0.6	15.8	12.6	+3.2	27.3	26.0	+1.3
Domain score ≥ 6 of 8*		1.1	1.0	+0.1	6.9	5.8	+1.1	1.3	0.7	+0.5	3.2	2.4	+0.8
Psychosocial	7												
Accomplish less than I used to		11.9	9.4	+2.5	21.0	20.2	+0.8	10.6	10.1	+0.5	20.8	21.6	−0.8
Experiencing poor memory		12.2	11.8	+0.4	21.3	22.3	−1.0	9.5	7.6	+1.9	16.7	14.9	+1.8
Feeling nervous or anxious		10.9	8.4	+2.5	19.4	20.2	−0.8	8.3	6.4	+1.9	16.8	14.8	+2.0
Domain score ≥ 6 of 8*		4.0	2.3	+1.7	3.7	2.3	+1.4	1.4	1.1	+0.3	2.7	1.7	+1.0

NOTE. "Bothersome" defined as symptom rated 6 to 8 out of possible 8 (8 anchored as "extremely bothersome"). Positive sign indicates excess in exemestane group
Abbreviation: MENQOL, Menopause-Specific Quality of Life Questionnaire.
*Based on all items in the domain.

limited. Still, the high compliance with quality-of-life assessments throughout the trial and the similarity of exemestane and placebo groups on key characteristics when comparing their baseline values with those at each later assessment is reassuring, and numbers for analyses were reasonable at 3 and 4 years after random assignment. In addition, because the 3-year exemestane intervention in the trial was sufficient to significantly reduce invasive breast cancers, our period of observation is clinically relevant. Finally, although we found no between-group difference in proportions "experiencing poor memory," this assessment based on a single MENQOL item is a limitation, given the concerns about cognitive effects among women who use endocrine therapies, and additional studies are clearly needed.

In summary, these results on the effects of exemestane on quality of life from a placebo-controlled randomized clinical trial inform clinical decision making for those contemplating breast cancer chemoprevention with exemestane. When selecting a chemoprevention agent, all risks and benefits should be considered. Although both tamoxifen and raloxifene reduce breast cancer and have little negative influence on quality of life,[19-21] their negative influence on venous thromboembolism and, for tamoxifen, on endometrial cancer limits their chemoprevention use in clinical practice.[22,23] With aromatase inhibitor use, bone loss and increased fractures are seen with the use of adjuvant aromatase inhibitors,[24] including use of exemestane.[25,26] However, in this MAP.3 trial at least, even though bone loss was seen,[25,26] fracture incidence was similar in both groups.[2] The International Exemestane Trial (IES) also found that bone mineral density rapidly recovered after exemestane use ended at trial completion.[27] Thus, long-term negative bone health influence may not pose a major barrier to short-term exemestane use. This information, considered along with the minimal negative effects on menopause-specific or health-related quality of life—effects which did not appear to affect women's perceptions of their own health or negatively affect their usual work or social activities—should reassure women and their clinicians regarding exemestane use in healthy postmenopausal women at higher risk for breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOSSARY TERMS

aromatase inhibitors: inhibitors used in treating breast cancer in postmenopausal women. Aromatase inhibitors inhibit the conversion of androgens to estrogens by the enzyme aromatase, thus depriving the tumor of estrogenic signals. Because of decreased production of estrogen, estrogen receptors, which are important in the progression of breast cancer, cannot be activated.

health-related quality of life (HRQoL): a broad multidimensional concept that usually includes self-reported measures of physical and mental health.

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Appendix

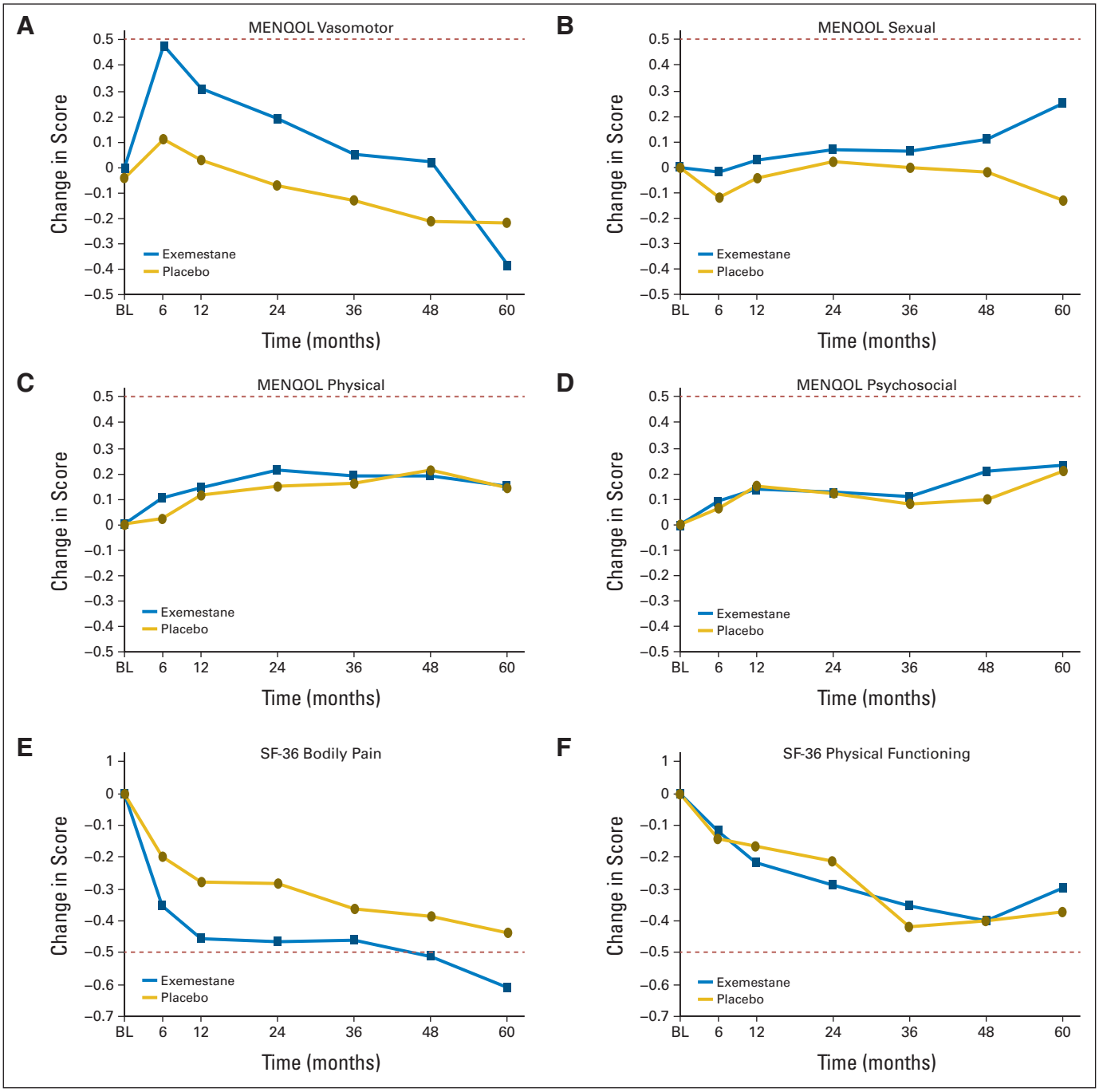

Fig A1. Mean changes in Menopause-Specific Quality of Life Questionnaire (MENQOL) and Medical Outcomes Study Short Form Health Survey (SF-36) scores relative to baseline, plotted in relation to each scale's threshold for potentially clinically meaningful changes (dotted red line).

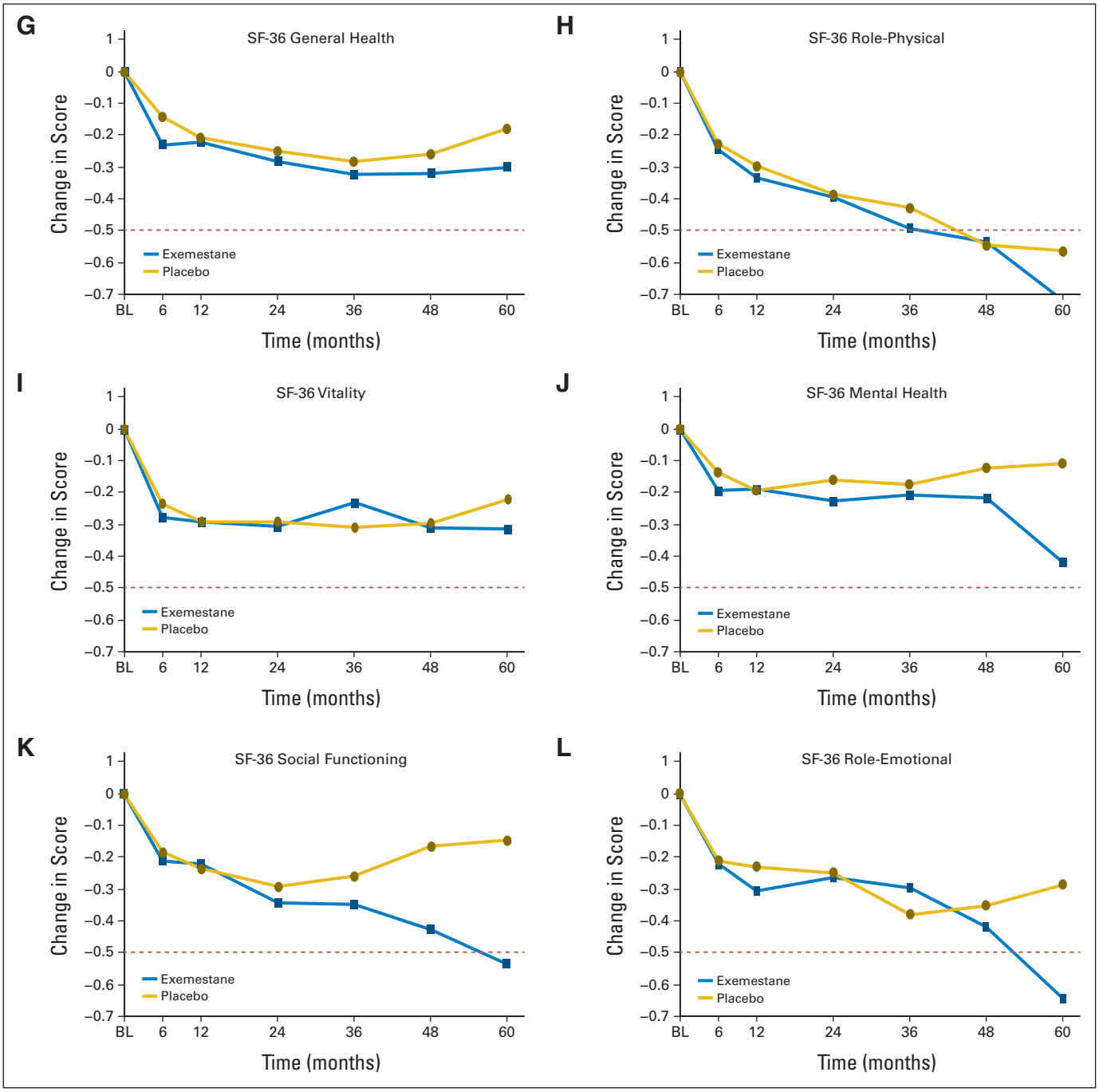

Fig A1. Continued.