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Original Article

Impact of Androgen Deprivation on Physical Well-Being in Patients With Prostate Cancer

Analysis From the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) Registry

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BACKGROUND: As androgen deprivation therapy (ADT) becomes a standard of treatment for men with recurrent or metastatic prostate cancer, evaluation of adverse effects associated with this treatment is needed. In this study, the authors evaluated the effect of ADT administered as monotherapy and in combination with local treatment on physical well-being in a longitudinal sample of men with prostate cancer. **METHODS:** Exposure to ADT was defined by 3 groups: local (local treatment only), combination (local treatment with adjuvant and/or neoadjuvant ADT), and primary ADT. Associations between exposure to ADT and physical well-being measured by self-reported health-related quality of life outcomes over time were evaluated by repeated measures analysis using mixed modeling. Estimates adjusted for various clinical and demographic variables are reported. **RESULTS:** A total of 2922 men, who completed both pretreatment and follow-up health-related quality of life assessment, were identified from the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) registry. During 24 months of follow-up, exposure to ADT was associated with worse physical well-being compared with local treatment at all time points ($P < .001$). Being exposed to ADT as primary therapy was associated with more severe declines compared with combination therapy. **CONCLUSIONS:** The potential consequence of decline in physical well-being in patients exposed to ADT has to be included in treatment decision making. ***Cancer* 2011;117:4406–13.** © *2011 American Cancer Society.*

KEYWORDS: prostate cancer, physical well-being, androgen deprivation therapy, CaPSURE.

Prostate cancer is among the most common cancers diagnosed in men. It was estimated that in 2010, 217,730 new cases of prostate cancer would be identified and 29,093 deaths would occur.[1] Older adults are disproportionally affected by this disease, with 75% of incidences and 90% of deaths occurring in men older than 65 years.[2] With successful treatment and increased survival, more men will live with consequences of the treatment while being at an increased risk for various morbidities. Moreover, older adults are more likely to have a higher number of comorbidities and decreased functional reserve; thus, the relative contribution of treatment's adverse effects to physical well-being may be paramount in the treatment decision process and successful survivorship.[3]

The primary goal of any treatment is to achieve optimal "physical, mental, and social well-being, not merely the absence of disease or infirmity."[4] Physical well-being, among the most important factors attributed to a person's level of independence, encompasses physical performance, functional capabilities, and energy level. In general, even relatively modest declines in functional capabilities are associated with loss of independence, increase in caregiver burden, and greater financial expenditures,[5] whereas better physical performance is associated with decrease in subsequent disability and better survival in older adults.[6] Health-related quality of life outcomes provide important information about effects of cancer treatment and subsequent survivorship. These outcomes can reflect symptoms related to fatigue and its sequelae, including loss of energy, restrictions in the ability to do daily activities, dizziness, and impaired cognitive function among many others.

Androgen deprivation therapy (ADT) is considered to be a standard treatment modality for men with recurrent and/or metastatic prostate cancer.[7] This treatment suppresses testicular androgen production and reduces estrogen, decreases

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tumor size, delays progression, and improves survival.[8] Androgen deprivation state can be achieved by orchiectomy (surgical castration) or medical castration with or without antiandrogen therapy. However, as use of ADT becomes more widespread, evaluation of the potential adverse effects associated with this treatment is imperative for treatment decision making and for ameliorating the impact of therapy on survivors' quality of life.[8-12] Major adverse effects of ADT that are attributed to decrease in estrogen levels include hot flashes and loss of libido.[10] Furthermore, numerous studies reported association of ADT with fatigue, decrease in bone mass, higher percentage of body fat, decrease in lean muscle mass, and increased incidence of fractures.[10,13-15] Recent studies described an increase in cardiovascular morbidity and mortality, but this association remains controversial.[16-18]

Several previous studies have reported on the effects of ADT on physical well-being. In the study by Levy et al, measurement of physical function, body composition, and visual-motor function demonstrated significant differences among men who underwent ADT therapy compared with other treatments.[9] Similarly, health-related quality of life outcomes have been shown to be severely impacted by ADT.[14,19-22] However, most studies evaluating effects of ADT on physical well-being have been limited to a small number of participants, have lacked pretreatment information, or have followed patients only to the immediate post-treatment period.

The goal of the present study was to evaluate the effects of ADT on physical well-being assessed by the physical function, role physical (limitation because of physical problems), vitality, and perceived general health subscales of the RAND 36-Item Short Form Health Survey (SF-36) over time in a diverse cohort of men with prostate cancer drawn from community-based practices at a wide range of geographical areas. We hypothesized that ADT affects physical well-being.

METHODS AND MATERIALS

Study Population

Data from CaPSURE (Cancer of the Prostate Strategic Urological Research Endeavor), a longitudinal, observational registry of men with biopsy-proven prostate adenocarcinoma, were used for this study. CaPSURE patients are recruited from 40 community-based, academic, and Veterans Affairs urology practices across the United States by participating urologists who report clinical data and follow-up information on diagnostic tests and treatments. Approximately 80% of patients are drawn from community-based practices in 25 states, ensuring a broad representation of geographically diverse community patients. Health-related quality of life data are obtained from a self-administered questionnaire mailed to each patient's home biannually. Patients are treated according to their physicians' usual practices and are followed until time of death or withdrawal from the study. Detailed descriptions of the CaPSURE study population and methodology have been published previously.[23,24]

Instrument

The self-administered SF-36 contains 8 subscales that assess physical, emotional, and social well-being, bodily pain, energy/fatigue, and general health perception domains.[25] Each subscale is scored from 0 to 100, with higher scores indicating better health-related quality of life. The reliability coefficients range from 0.80 to 0.95 and from 0.68 to 0.91 among patients with prostate cancer.[26,27]

Assessment of Physical Well-Being

Physical well-being of the participants in the CaPSURE registry is evaluated by physical function, role physical (limitation because of physical problems), vitality, and perceived general health (GH) subscales. These subscales assess the degree to which respondents had difficulties with physical activities (including lifting, climbing, bending), were restricted in their regular daily activities or work, and felt tired or worn out, and their perception of health during the previous 4 weeks.

Exposure Assessment

ADT exposure was defined by evaluation of initial treatment and adjuvant and/or neoadjuvant therapy. Patients who underwent only radical prostatectomy, external beam radiation, or brachytherapy were considered to be in the Local group, patients who underwent the same treatments with the addition of ADT (either as adjuvant or neoadjuvant therapy) were considered to be in the Combination group, and patients whose initial treatment consisted of ADT monotherapy (medical or surgical castration, with or without antiandrogen therapy) were considered to be in the Primary ADT group. The duration of ADT was determined by the clinical practice of the treating physician and was categorized as receiving ADT for <6 months and receiving ADT for ≥ 6 months.

Covariates

The covariates in our analyses included sociodemographic, lifestyle-related, and clinical prognostic factors

that based on the existing literature can potentially confound or modify association between exposure to ADT and physical well-being.[28-31] The sociodemographic covariates included age (evaluated by 2 separate variables: age at diagnosis categorized as <65, 65-75, and >75 years; and age at each health-related quality of life assessment) and annual income, categorized as <$30,000, $30,000-$50,000, $50,000-75,000, and > $75,000. Lifestyle-related factor included body mass index (BMI) categorized as <25.0, 25.0-29.9, and >30 kg/m^2. Risk of prostate cancer recurrence was assessed by a modification of the D'Amico risk classification[32] in which low risk was defined as clinical stage T1 or 2a, Gleason score <7, prostate-specific antigen (PSA) level <10 ng/mL; intermediate risk as stage T2b, Gleason score 7, or PSA between 10 and 20 ng/mL; and high risk as any stage greater than T2b, Gleason score >7, or PSA level >20 ng/mL. Comorbidities were assessed from a self-reported checklist completed upon enrollment in the study that includes 11 categories of common conditions. Numbers of comorbidities were summed into a 3-level categorical variable (none, 1-2, and >3).

Statistical Methods

We examined the distribution of the independent and dependent variables for missing and out of range values, evaluated underlying assumptions of the statistical models, and assessed collinearity among variables of interest. Pretreatment demographic and clinical characteristics were compared across 3 treatment groups, with analysis of variance (ANOVA) for continuous variables and chi-squared analyses for categorical variables. In case of non-normal distribution, a nonparametric (Kruskal-Walis) test was used. Welch ANOVA was used to adjust for unequal group variances. Association of pretreatment health-related quality of life with clinical and demographic variables was evaluated by ANOVA. Repeated measures analysis with mixed modeling was implemented. This analysis was chosen because it accounts for between- and within-subjects variability while evaluating whether changes in physical well-being differ among treatment group over time. In addition, a mixed model optimally handles missing data by accounting for the time patterns in available data.

Health-related quality of life was assessed at pretreatment and 6, 12, 18, and 24 months after initiation of primary treatment. Covariates included pretreatment age at diagnosis, risk of prostate cancer recurrence, time of assessment, number of comorbid conditions, BMI categories, income, and age at each health-related quality of life assessment. Age at diagnosis and age at each health-related quality of life assessment were highly correlated; thus, each of these variables was examined separately. Interaction between treatment group and time of assessment was tested to examine whether treatment had different effects on health-related quality of life over time. Two-sided $P <$ .05 was considered to determine statistical significance. All analyses were performed using version 9.2 of SAS for Windows (SAS Institute, Cary, NC).

RESULTS

As of June 2009, 13,821 patients were enrolled in CaPSURE. Of these, 6698 were newly diagnosed (ie, enrolled within 6 months of diagnosis) and had information on their initial treatment. When the inclusion criteria of having pretreatment and at least 2 post-treatment assessments were applied, 2922 men constituted the study population. Of these men, 71.7% were not exposed to ADT, 22.07% had combination treatment, and the remaining 6.2% underwent primary ADT. Among men in the primary ADT group, 66.7% were treated with monotherapy, with remainder undergoing combined androgen blockade. A greater proportion of men in both the primary ADT and the combination group had been receiving ADT for <6 months (76.8% and 78.3%, respectively). Men in the primary ADT group were older, had a higher risk of prostate cancer recurrence, and reported more comorbidities (see Table 1). General health-related quality of life at pretreatment differed based on the treatment group, with men in the primary ADT group demonstrating much lower scores compared with men who were not exposed to ADT or were treated with combination therapy (unadjusted means and standard deviations are presented in Table 2). Lower physical function, role physical, and GH at pretreatment continued to be associated with exposure to ADT even after accounting for age at diagnosis, risk of prostate cancer recurrence, number of comorbidities, and BMI (Table 3).

Multivariate repeated measures analysis demonstrated that exposure to ADT was associated with a significant decline in physical function, role physical, vitality, and GH while controlling for pretreatment level of physical function, role physical, vitality, GH, age at diagnosis, risk of prostate cancer recurrence category, race, BMI, and number of comorbidities. Additional analyses controlling for age at each health-related quality of life assessment were undertaken. Results were similar to the model that included age at diagnosis only and thus are not reported. Men treated with primary ADT therapy experienced a

Table 1. Clinical and Sociodemographic Characteristics of Study Population[a]

Study Characteristic	Value	Primary ADT		Combination		Local		P^b
		No.	%	No.	%	No.	%	
Age at diagnosis, y	<65	26	15	154	27	1243	57	<.01
	65-75	61	34	290	51	793	36	
	>75	90	51	123	22	137	6	
Clinical risk category	Low	46	27	155	28	1102	54	<.01
	Intermediate	56	33	205	37	681	33	
	High	67	40	191	35	273	13	
Number of comorbidities	0	17	10	67	12	372	17	<.01
	1-2	71	40	307	54	1238	57	
	>3	89	50	193	34	563	26	
Household income	<$30,000	71	40	184	32	387	18	<.01
	$30-50,000	42	24	127	22	465	21	
	$50-75,000	29	16	103	18	418	19	
	>$75,000	18	10	92	16	769	35	
	Unknown	17	10	61	11	134	6	
Race/ethnicity	Black	15	8	38	7	94	4	.02
	White	154	87	512	90	2020	93	
	Other/mixed/unknown	8	5	17	3	59	3	
Education level	<HS	38	21	95	17	176	8	<.01
	HS graduate	89	50	263	46	911	42	
	College graduate	50	28	209	37	1086	50	
BMI	Not overweight	55	31	145	26	562	26	.15
	Overweight	76	43	283	51	1136	53	
	Obese	44	25	131	23	454	21	

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; HS, high school.
[a] Numbers may not equal the total study sample due to missing data.
[b] *P* values were computed using chi-square tests, testing the difference between pretreatment clinical and demographic characteristics by each treatment group.

Table 2. Unadjusted Pretreatment Health-Related Quality of Life by Treatment Group

Subscale	Primary ADT		Combination		Local		Welch's ANOVA
	Mean	SD	Mean	SD	Mean	SD	
Physical function	75.31	24.01	82.12	21.91	89.25	17.56	<.001
Role physical	65.53	42.98	75.21	37.38	84.55	31.28	<.001
General health	63.53	20.71	71.19	19.02	75.04	18.16	<.001
Vitality	62.09	19.43	66	19.85	68.94	18.55	<.001

Abbreviations: ADT, androgen deprivation therapy; ANOVA, analysis of variance; SD, standard deviation.

significant decline in physical function, role physical, GH, and vitality (ranging from 8.9 to 13.8 points) over a period of 24 months (see Table 4). Similarly, men undergoing combination therapy demonstrated declines in all 4 outcomes, although magnitude of the effect was smaller (Table 4).

Significant interaction between treatment and time of the assessment was noted, suggesting that patterns of responses varied among treatment groups over time. In general, all 3 treatment groups displayed a significant decline in health-related quality of life after treatment. However, men not exposed to ADT and those treated with combination therapy demonstrated gradual improvements, whereas men treated with primary ADT steadily declined in all 4 domains over the 2-year follow-up. Health-related quality of life trends for role physical, vitality, physical function, and GH are provided in Figures 1 to 4.

Having a greater number of comorbid conditions and lower household income and being in a higher BMI category (all at $P < .001$) were associated with decline in all 4 domains. Furthermore, higher risk of recurrence was associated with decline in physical function, role physical, and GH, but not vitality. Age at diagnosis was significantly ($P = .05$) associated with declines in physical function, role physical, and GH, but not vitality.

Table 3. Adjusted Pretreatment HRQOL by Treatment Group[a]

Subscale	Primary ADT		Combination		Local	
	Mean	SE	Mean	SE	Mean	SE
Physical function	80.10	1.49	83.01	0.83	84.95	0.58
Role physical	72.94	2.75	76.42	1.50	79.03	1.03
General health	67.37	1.43	72.90	0.81	74.27	0.57
Vitality	65.19	1.48	66.95	0.83	67.50	0.59

Abbreviations: ADT, androgen deprivation therapy; HRQOL, health-related quality of life; SE, standard error.
[a] Fully adjusted models included age, household income, clinical risk classification, body mass index, number of comorbid conditions, time of the HRQOL assessment, and interaction term between treatment group and time of the HRQOL assessment.

Table 4. Repeated Measures Analysis With Mixed Modeling[a] Evaluating Association Between Treatment Type and Physical Well-Being Over 24 Months

Treatment Group	Physical Function		Role Physical		General Health		Vitality	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Primary ADT	−13.83	1.76	−15.57	3.36	−10.70	1.68	−8.92	1.77
Combination	−3.93	1.01	−3.85	1.89	−2.95	0.97	−2.13	1.01
Local	Reference		Reference		Reference		Reference	

Abbreviations: ADT, androgen deprivation therapy; SE, standard error; HRQOL, health-related quality of life.
[a] Fully adjusted models included age, household income, clinical risk classification, body mass index, number of comorbid conditions, time of the HRQOL assessment, and interaction term between treatment group and time of the HRQOL assessment.

DISCUSSION

The objective of this study was to evaluate the effects of ADT on physical well-being over time using longitudinal observational data from CaPSURE. The results show that pretreatment physical well-being domains were worse in patients treated with primary ADT and were associated with age at diagnosis, risk for cancer recurrence, and number of comorbidities. During the 2-year follow-up, men treated with ADT had greater decline in all domains related to physical well-being. Whereas men in local and combination groups demonstrated slow recovery after initial decline, men in the primary ADT group experienced steady declines.

Although it has been previously reported that health-related quality of life is significantly associated with various clinical and demographic factors such as age, comorbid conditions, and clinical presentation, our findings suggests that treatment, especially ADT, has an independent effect on physical well-being. These findings are consistent with some of the previous studies that demonstrated declines in 1 or more aspects of physical health in patients receiving ADT.[9,19,33] Dacal et al reported that men receiving ADT had significantly poorer physical function and general health, which was reflected by lower physical health component score. However, after controlling for significant joint predictors of comorbidity and total testosterone, they concluded that these 2 factors, and not ADT, contributed to the difference in physical health component summary.[19] Considering several limitations of this study, such as the small sample size (n = 96), presence of hypogonadal participants in the control group, and possible mediating affect of testosterone on physical function, the independent effect of ADT on physical well-being continued to be a topic of interest in that study. Similarly, in a study of 3144 Medicare beneficiaries who reported cross-sectional, age-adjusted health-related quality of life responses to treatment, concerns over body image, mental health, general health, activities, and worry about cancer demonstrated significant decrements in men undergoing ADT compared with active treatment only.[33]

Although there were differences in magnitude, results from this study suggest that both primary and combination use of ADT is associated with a decline in physical well-being in most patients. Patients undergoing multimodal therapy reported having worse health-related quality of life compared with monotherapy,[21,34] whereas ADT significantly affected physical function compared with active treatments.[10,35,36] Given differences in scores at pretreatment and the lower magnitude of the decline, it is reasonable to suggest that combination therapy influences physical well-being to a smaller degree compared with ADT alone, but nevertheless these effects have to be

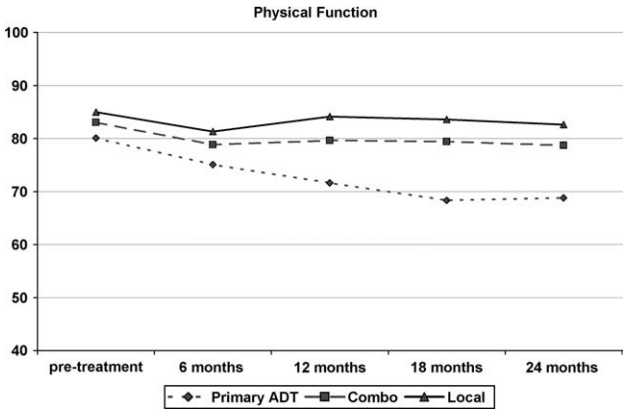

Figure 1. Longitudinal changes in physical function are shown from pretreatment to 2-year follow-up in 3 treatment groups. Abbreviation: ADT, androgen deprivation therapy.

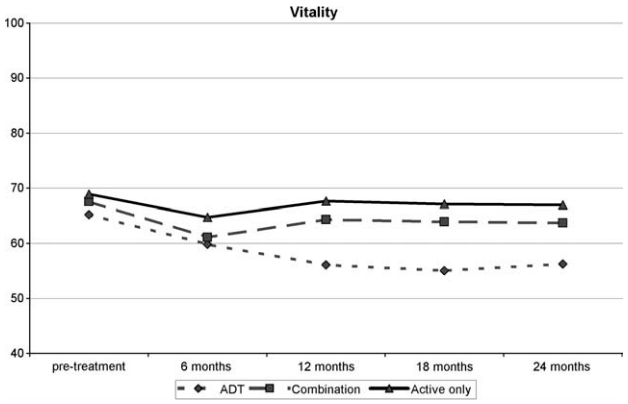

Figure 3. Longitudinal changes in vitality are shown from pretreatment to 2-year follow-up by 3 treatment groups. Abbreviation: ADT, androgen deprivation therapy.

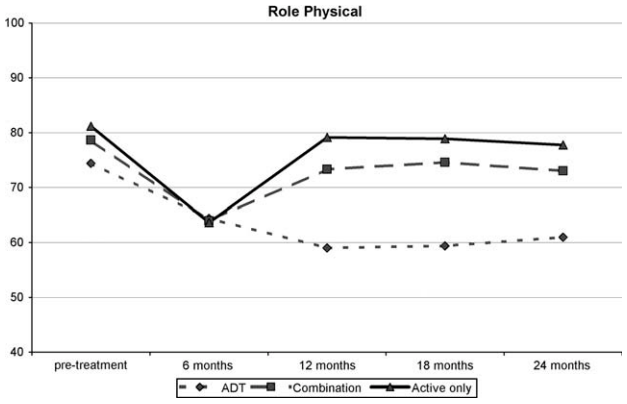

Figure 2. Longitudinal changes in role physical are shown from pretreatment to 2-year follow-up in 3 treatment groups. Abbreviation: ADT, androgen deprivation therapy.

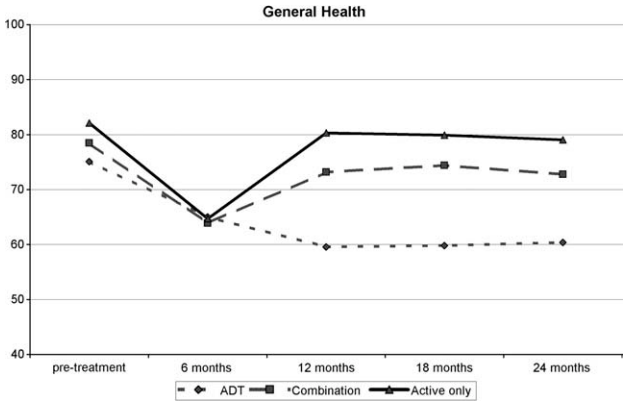

Figure 4. Longitudinal changes in general health are shown from pretreatment to 2-year follow-up by 3 treatment groups. Abbreviation: ADT, androgen deprivation therapy.

considered in the treatment decision process for both treatment modalities.

Although several studies have reported on the adverse effect of ADT on health-related quality of life, a majority of the studies had limited clinical and demographic baseline information and used a cross-sectional approach. Although similar to previous reports in that a greater number of comorbidities, older age, higher risk of recurrence, and lower socioeconomic status were significantly associated with worse health-related quality of life, in the current study, the independent effect of ADT continued to be related to worse physical well-being after adjustment for multiple covariates.

It should be noted that age plays a significant role in evaluation of the health-related quality of life. Age-related changes in physical and physiological reserve, such as fatigue and increased risk of falling, could lead to significant declines of overall physical well-being.[36,37] In addition, age and life expectancy play important roles in treatment choices and subsequent recovery.[38] Still, even when controlling for both age at diagnosis and age at each assessment, ADT demonstrated a strong association with declines in physical function and vitality in our study.

Several limitations to our study should be noted. Because of the observational nature of the CaPSURE registry, selection and observational bias is possible. In addition, patients are enrolled by their treating urologists; thus, the predominance of patients undergoing prostatectomy as an initial treatment is evident. Participants treated with primary ADT were more likely to have insufficient pretreatment and post-treatment assessment and thus represented a smaller proportion of the study population. The comorbidity assessment in CaPSURE does not account for the severity of key comorbidities, which may

impact health-related quality of life to a varying extent. However, we plan on using an expanded measure (Total Illness Burden Index for Prostate Cancer [TIBI-CaP]) in future studies. Moreover, this registry lacks data on measures of specific activities of daily living that directly measure physical function, factors associated with treatment decision making process, and biological information, such as serum androgens and specific body composition measurements. Whereas we chose to concentrate on physical well-being in this study, we plan to expand our analysis to the cognitive changes that are attributed to ADT use in future studies. We also plan to apply methods to estimate minimal clinically important differences in addition to the changes over time presented in this paper.

However, this study has several important strengths. The population of CaPSURE consists of patients receiving medical care from a geographically diverse set of primarily community-based practices, reflecting patterns of usual care for patients with prostate cancer. Use of validated, widely used questionnaires provides us with an important self-evaluation of physical well-being. Availability of the pretreatment and follow-up measures of health-related quality of life, ability to control for many pretreatment characteristics, and availability of longitudinal observation offer a unique opportunity to evaluate health-related quality of life over a period of time that encompasses diagnosis, treatment, and survivorship of prostate cancer patients.

In conclusion, it was observed that the physical well-being of men receiving ADT was adversely affected, even when accounting for important clinical and demographic factors. Such declines have to be considered in the treatment decision process.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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